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(54) Title: ANTIBODIES AGAINST HUMAN CD40

#### (57) Abstract

The Applicants have discovered novel chimeric and humanized anti-human CD40 antibodies which block the interaction between gp39 and CD40. The anti-CD40 antibodies of the present invention are effective in modulating humanic immune responses against T cell-dependent antigens, collagen induced arthritis, and skin transplantation, and are also useful for their anti-inflammatory properties.

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# ANTIBODIES AGAINST HUMAN CD40

### 5 Background of the Invention

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Immune/inflammatory responses are mediated by a complex series of interactions. One receptor/ligand pair shown to be important in these processes is CD40/gp39. The gp39/CD40 interaction mediates a number of important signaling events between activated T cells and other effector cells of the immune system leading to amplification of an immune/inflammatory response. Responses to signaling through CD40 include T cell help to B cells in the humoral immune response, induction of cytokines by monocytes, and expression of adhesion molecules by endothelial cells.

CD40 is a type I cell surface receptor and a member of the tumor necrosis factor receptor (TNFR) supergene family. Though originally identified as a B cell antigen, CD40 is now believed to be expressed by all antigen presenting cells (APC), including dendritic cells, keratinocytes, and monocytes. CD40 is also expressed by cell types that can act as APC under certain conditions, such as vascular endothelial cells, or cells involved in direct interactions with T cells or T cell precursors such as thymic epithelial cells. More recently, it has also been reported that CD40 can be expressed by fibroblasts, eosinophils, and activated T cells. CD40 expression has also been seen in cancerous cells. Evidence for this is primarily derived from the identification of some carcinoma and melanoma derived cell lines which are CD40<sup>+</sup>. (Clark and Ledbetter, Proc. Natl. Acad. Sci. (1986) 83:4494-98; Schriever et al., J. Exp. Med. (1989) 169:2043-58; Caux et al., J. Exp. Med. (1994) 180:1263-72; Alderson et al., J. Exp. Med. (1993) 178:669-74; Young et al., Int. J. Cancer (1989) 43:786-94; Paulie et al., Cancer Immunol. Immunother. (1985) 20:23-28; Denfeld et al., Eur. J. Immunol. (1996) 26:2329-34; Gaspari et al., Eur. J. Immunol. (1996) 26:1371-77; Peguet-Navarro et al., J. Immunol. (1997) 158:144-52; Hollenbaugh et al., J. Exp. Med. (1995) 182:33-40; Galy and Spits, J. Immunol. (1992) 149:775-82;

T cells. Gp39 is also known as CD40L, TRAP, T-BAM, and now has the official CD designation from the Leukocyte Workshop of CD154. In *in vitro* assays, gp39 appears on the T cells approximately 2-4 hours following T cell activation and levels peak at 6-8 hours. The protein level then rapidly declines and is undetectable 24 hours after stimulation. Gp39 expression has also been detected on eosinophils and mast cells. (Noelle et al., Proc. Natl. Acad. Sci. (1992) 89:6550-54; Hollenbaugh et al., EMBO J. (1992) 11:4313-21; Spriggs et al., J. Exp. Med. (1992) 176:1543-50; Graf et al., Eur. J. Immunol. (1992) 22:3191-94; Covey et al., Mol. Immunol. (1994) 31:471-84; Castle et al., J. Immunol. (1993) 151:1777-88; Roy et al., J. Immunol. (1993) 151:2497-2510; Gauchat et al., Nature (1993) 365:340-43; Gauchat et al., Eur. J. Immunol. (1995) 25:863-65; Koshy et al., J. Clin. Invest. (1996) 98:826-37; Desai-Mehta et al., J. Clin. Invest. (1996) 97:2063-73).

CD40 is a potent signaling receptor, providing a mechanism for activated T-cells to regulate a wide range of immune and inflammatory responses. *In vitro* and *in vivo* studies with recombinant forms of the gp39 ligand and with anti-CD40 mAbs have shown that signaling through this receptor leads to a cellular response in all known CD40<sup>+</sup> cells, and that outcome not only varies by cell type but is also modulated by concurrent signaling events through other receptors. In B cells, for example, CD40 signaling in conjunction with signaling by the IL-4 receptor leads to B cell proliferation and production of antibodies of the IgE isotype, while CD40 signaling in conjunction with signals from the IL-10 receptor lead to B cell proliferation and production of antibodies of the IgG isotype (Gordon et al., Eur. J. Immunol. (1987) 17:1535-38; Rousset et al., J. Exp. Med. (1991) 173:705-710; Jabara et al., J. Exp. Med. (1990) 172:1861-64; Gascan et al., J. Immunol. (1991) 147:8-13). Gp39 mediated CD40 signaling may play a role in cellular immunity through the induction of CD80 and CD86, important T cell costimulatory molecules which bind CD28 and CTLA4 (Goldstein et al., Mol. Immunol. (1996) 33:541-52).

The CD40/gp39 receptor/ligand system is one of the many systems which are involved in the productive interaction between activated T cells and other cells of the immune system. However, a number of findings suggest that this interaction is unique and central to the regulation of the humoral immune response in humans. In

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particular, defects in gp39 expression or structure have been shown to be the cause of the human immunodeficiency known as X-linked hyper IgM (X-HIM) syndrome. This immunodeficiency is characterized by the inability of affected individuals to produce antibodies other than those of the IgM isotype, indicating that the productive interaction between gp39 and CD40 is required for an effective humoral immune response (Allen et al., Science (1993) 259:990-93; Aruffo et al., Cell (1993) 72:291-300; Di Santo et al., Nature (1993) 361:541-43; Fuleihan, et al., Proc. Natl. Acad. Sci. (1993) 90(6):2170-73; Korthauer et al., Nature (1993) 361:539-541; Notarangelo et al., Immunodef. Rev. (1992) 3:101-22). Likewise, recent data indicate that non-Xlinked HIM syndrome in humans is caused by defects in the CD40 molecule. Using gene knockout technology, mice lacking CD40 or gp39 have been generated. These mice exhibit a phenotype which has the same characteristics as HIM syndrome suggesting that mice can be an appropriate model in which to test the effects of in vivo treatment with either anti-CD40 or anti-gp39 mAbs that block the interaction between CD40 and gp39 (Kawabe et al., Immunity (1994) 1:167-78; Xu et al., Immunity (1994) 1:423-431; Renshaw et al., J. Exp. Med. (1994) 180:1889-1900; Castigli et al., Proc. Natl. Acad. Sci. USA (1994) 91:12135-39).

The effects of *in vivo* inhibition of the CD40/gp39 interaction have been extensively studied in normal mice and mouse models of disease using a hamster antimouse gp39 mAb (MR1). The immunosuppressive capacity of the antibody is reflected in its ability to completely inhibit the humoral immune response to T-cell dependent antigens (Foy, et al., <u>J. Exp. Med.</u> (1993) 178:1567-75). Several mouse models of immune diseases have also been shown to be inhibited by treatment with the antibody, including those mediated by cellular immune responses. Disease models shown to be inhibited by treatment with anti-gp39 include collagen induced arthritis, experimental allergic encephalomyelitis, lupus nephritis, transplant rejection, and graft vs. host disease (Durie et al., <u>Science</u> (1993) 261:1328-30; Berry, et al., unpublished; Gerritse et al., <u>Proc. Natl. Acad. Sci. USA</u> (1995) 93:2499-504; Mohan et al., <u>J. Immunol.</u> (1995) 154:1470-1480; Larsen et al., <u>Transplantation</u> (1996) 61:4-9; Hancock et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996) 93:13967-72; Parker et al., <u>Proc. Natl. Acad. Sci. USA</u> (1996)

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94:1333-38; Wallace, et al., unpublished). The role of CD40/gp39 in the amplification of a cellular immune response may be direct, through the stimulation of a subset of activated T cells that are capable of expressing CD40, or indirect, through induction of cytokines and the expression of important co-stimulatory cell surface molecules such as CD80 and CD86, which bind to the T cell receptors CD28 and CTLA-4. The anti-inflammatory effects of the inhibitor have been demonstrated by studies in a mouse model of oxygen-induced lung injury. The effects on inflammation *in vivo* are suggested by the *in vitro* results demonstrating stimulation of CD40 on vascular endothelial cells and monocytes which results in the expression of cell adhesion molecules, nitric oxide (NO), matrix metalloproteinases and proinflammatory cytokines (Kiener et al., <u>J. Immunol.</u> (1995) 155:4917-25; Malik et al., <u>J. Immunol.</u> (1995) 156:3952-60; Hollenbaugh et al., <u>J. Exp. Med.</u> (1995) 182:33-40).

Studies with anti-human gp39 mAbs in monkeys have shown that biologics which inhibit the interaction between gp39 and CD40 *in vivo* are effective immunosuppressive agents in primates. Anti-gp39 mAbs have been demonstrated to be effective in the inhibition of antibody responses to T-cell dependent antigens, and to protect allografts from rejection, results analogous to that seen in rodents.

Collectively the above studies have shown that agents which disrupt the interaction between gp39 and CD40 would be potent immunosuppressive and anti-inflammatory agents. Therefore, there exists a need in the art for an effective method of blocking the CD40/gp39 interaction to provide an immunosuppressive or anti-inflammatory effect. A purpose of the present invention is to provide an antibody which blocks the interaction between gp39 and CD40.

Another object of the present invention is to provide a chimeric antibody effective in blocking the interaction between CD40 and gp39.

An additional object of the present invention is to provide a humanized antibody effective in blocking the interaction between CD40 and gp39.

A further object of the present invention is a method of modulating an immune response by administering an antibody, chimeric antibody, or humanized antibody of

the present invention. The method may be useful in treating any number of autoimmune diseases, as well as skin or other organ transplantation.

# Summary of the Invention

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The present invention comprises a novel antibody, more preferably a chimerized anti-human CD40 monoclonal antibody (mAb), which blocks the interaction between gp39 and CD40. In one embodiment of the present invention, a particularly preferred chimerized anti-human CD40 mAb is referred to as "chi220". Chi220 is a chimeric antibody comprising murine variable and human kappa and gamma 1 constant regions. Chi220, like its parent mouse mAb, binds to CD40 and, as a result, effectively blocks humoral immune responses to T cell-dependent antigens in a dose dependent fashion.

Also encompassed within the scope of the present invention are humanized anti-CD40 antibodies which block the interaction between gp39 and CD40. In one embodiment of the present invention, a humanized antibody is referred to as F4; in another embodiment the humanized antibody is referred to as L3.17. The preferred humanized antibodies of the present invention comprise human variable heavy and variable light regions with murine CDR's grafted therein.

The anti-CD40 antibodies of the present invention, preferably the chimeric and humanized antibodies disclosed herein, are effective in modulating humanized immune responses against T cell-dependent antigens, collagen induced arthritis, and transplant rejection. The anti-CD40 antibodies of the present invention, preferably the chimeric and humanized antibodies disclosed herein, are also useful for their anti-inflammatory properties (which are similar to those seen with anti-gp39).

The antibodies of the present invention, particularly the anti-CD40 chimeric antibody chi220 and the anti-CD40 humanized antibodies F4 and L3.17, have wide therapeutic applications, including autoimmune diseases, inflammatory diseases and transplantation. Because of the expression of CD40 seen on malignant cells of several histologic types, the potential oncology applications of anti-CD40 antibodies, particularly the chimeric and humanized antibodies of the present invention, are evident.

The following abbreviations are used throughout the present application and are known by those skilled in the art: APC (antigen presenting cell); CDR (complemenrarity- determining region); CHO (chinese hamster ovary); CIA (collagen-induced arthritis); Cmax (maximum serum concentration); COS (African green monkey fibroblast cell line); DMARD (disease modifying anti-rheumatic drugs); ELISA (enzyme-linked immunosorbent assay); EPT (end point titers); EU (endotoxin units); Fab (antigen binding fragment); FITC (fluoroisothiocyanate); Hu (humanized); h106-2 (humanized anti-gp39 mAb); HAMA (human-anti-mouse antibodies); im (intramuscular); KLH (keyhole limpet hemocyanin); mAb (monoclonal antibody); MTX (methotrexate); OVA (ovalbumin); PBS (phosphate buffered saline); PCR (polymerase chain reaction); PE (phycoerytherin); sc (subcutaneous); SDS-PAGE (sodium dodecyl sulfate polyacrylamide gel electrophoresis); SEC (size exclusion chromatography); SRBC (sheep red blood cells); STR (stirred tank reactor); TNF (tumor necrosis factor); VL (antibody light chain variable region); VH (antibody heavy chain variable region).

A nucleic acid encoding a preferred light chain of a chimeric antibody of the present invention (chimeric antibody 2.220) has been deposited with the American Type Culture Collection and given the Accession Number ATCC \_\_\_\_\_. A nucleic acid encoding a preferred heavy chain of a chimeric antibody of the present invention (2.220) has been deposited with the American Type Culture Collection and given the Accession Number ATCC \_\_\_\_\_.

A nucleic acid encoding a preferred light chain of a humanized antibody of the present invention (humanized antibody F4) has been deposited with the American Type Culture Collection and given the Accession Number ATCC \_\_\_\_\_\_. A nucleic acid encoding an additional preferred light chain of a humanized antibody of the present invention (humanized antibody L3.17) has been deposited with the American Type Culture Collection and given the Accession Number ATCC \_\_\_\_\_\_. A nucleic acid encoding a preferred heavy chain of a humanized antibody of the present invention (F4 and L3.17) has been deposited with the American Type Culture Collection and given the Accession Number ATCC \_\_\_\_\_.

The deposit(s) referred to herein will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-Organisms for purposes of Patent Procedure. These deposits are provided merely as convenience to those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112. The sequence(s) of the polynucleotides contained in the deposited materials, as well as the amino acid sequence of the polypeptides encoded thereby, are incorporated herein by reference and are controlling in the event of any conflict with any description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

All references cited in this application, whether *supra* or *infra*, are herein incorporated by reference in their entirety.

# Brief Description of the Drawings

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Figure 1 shows the inhibition of sgp39 binding to Raji cells by anti-human CD40 mAbs.

Figure 2 is a schematic outlining the primate study protocol. Days of treatment are indicated with diamonds. Immunizations with SRBC and KLH are indicated with rectangles and triangles, respectively. Animals treated with 2.36 were not studied past Phase I and animals treated with 1.106 were not studied past Phase II.

Figure 3 shows the anti-SRBC antibody response in primates. Figure 3a shows the results of analysis for IgM anti-SRBC antibodies. Figure 3b shows the results of analysis for IgG anti-SRBC antibodies.

Figure 4a shows the sequence of the light chain variable region of chi220 in bold (SEQ ID NO:1), and Figure 4b shows the sequence of the heavy chain variable region of chi220 in bold (SEQ ID NO:2). The underlined sequences in Figure 4a and 4b are the inserted signal sequences of the human antibody with the closest homology which had been used as humanization template.

Figure 5 shows the results of *in vitro* assays testing chimeric and humanized antibody of the present invention. Figure 5a shows the binding of chi220 and h220v3 to hCD40-mG2b in an ELISA based assay. Figure 5b shows the inhibition of sgp39-mediated costimulation of human B cells with anti-human CD40 mAbs.

Figure 6 shows the IgM Anti-SRBC antibody response. Figure 6a shows the results from monkeys that received 10, 40 or 100 mg/kg chi220. Figure 6b shows the results from monkeys that received 0.1 or 1 mg/kg chi220.

Figure 7 shows the IgG Anti-SRBC antibody response. Figure 7a shows the results from monkeys that received 10, 40 or 100 mg/kg chi220. Figure 7b shows the results from monkeys that received 0.1 or 1 mg/kg chi220.

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Figure 8 shows the anti-OVA antibody response in primates. Figure 8a shows the results of analysis for IgM anti-OVA antibodies. Figure 8b shows the results of analysis for IgG anti-OVA antibodies.

Figure 9 shows the anti-KLH antibody response in primates. Figure 9a shows the results of analysis for IgM anti-KLH antibodies. Figure 9b shows the results of analysis for IgG anti-KLH antibodies.

Figure 10 shows a comparison of the ability of antibody 7E1-G1 and 7E1-G2b to suppress an IgG antibody response to SRBC.

Figure 11 shows the dose response of inhibition of antibody response to SRBC with 7E1-G2b.

Figure 12 shows expression vector maps for a heavy chain region and light chain region of a chimeric antibody of the present invention.

Figure 13 provides a nucleic acid sequence for an expression vector capable of expressing a heavy chain of a chimeric antibody of the present invention. The start ATG (nucleotides 1000-1002), encoding the start Met of the inserted signal sequence of the human antibody, is in bold. Nucleotides 1057 through 1422 (SEQ ID NO:5), underlined, provide a preferred nucleic acid sequence encoding a variable heavy chain of an antibody of the present invention.

Figure 14 provides a nucleic acid sequence for an expression vector capable of expressing a light chain of a chimeric antibody of the present invention. The start ATG (nucleotides 1005-1007), encoding the start Met of the inserted signal sequence of the human antibody, is in bold. Nucleotides 1065 through 1388 (SEQ ID NO:6), underlined, provide a preferred nucleic acid sequence encoding a variable light chain of an antibody of the present invention.

Figure 15 shows an alignment of murine anti-CD40 variable regions and a human template sequences. The amino acid sequences of the murine anti-CD40 H and L chain variable regions were used to identify homologous human germline sequences. The numbering of residues and the definition of CDRs (underlined) were based on Kabat et al. (Kabat, E.A., et al., (1991) Sequences of proteins of immunological interest (5th Ed). Washington DC: United States Department of Health and Human Services; Kabat, E.A., et al., (1977) *J. Biol. Chem.* 252:6609-6616). Differences in sequence are indicated by vertical lines and framework positions characterized in the combinatorial expression library are marked with an asterisk.

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Figure 16 shows the results of titration of humanized anti-CD40 variants on immobilized antigen. Bacterially-expressed chimeric anti-CD40 Fab and select variants from each of the libraries were characterized. Chimeric (filled circles), Hu I-19C11 (open circles), Hu II-CW43 (open squares), Hu III-2B8 (filled triangles), and an irrelevant (filled squares) Fab were released from the periplasmic space of 15 ml bacterial cultures and serial dilutions were incubated with CD40-Ig antigen immobilized on microtiter plates. Antibody binding was quantitated as described below.

Figure 17 demonstrates how antibody affinity correlates with the inhibition of soluble-gp39 binding to CD40-Ig. The ligand for the CD40 receptor, gp39, was captured in a microtiter plate. Subsequently, varying amounts of purified chimeric (filled circles), Hu II-CW43 (open squares), Hu III-2B8 (filled triangles), Hu II/III-2B12 (open circles), and irrelevant (filled squares) Fab were co-incubated with 2  $\mu$ g/ml CD40-Ig on the microtiter plate. Binding of CD40-Ig to gp39 was quantitated as described below.

Figure 18 shows the quantitation of murine framework residues in active variants. The variable regions of the most active anti-CD40 variants from the framework optimization library Hu I (A) and from the framework/HCDR3 optimization library Hu II (B) were sequenced to identify the amino acids at framework library positions. Each unique variant was categorized based on the total number of murine residues retained at the 8 framework library positions. Thirty-four

clones from the Hu I library and fourteen clones from the Hu II library were sequenced, leading to the identification of 24 and 10 unique variants, respectively. The solid line indicates the sequence distribution expected from an equal number of randomly selected variants.

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# Detailed Description of the Invention

The present inventors have developed chimeric and humanized anti-human CD40 antibodies with immunosuppressive properties. Such anti-human CD40 antibodies have obvious applications as a therapeutic. The present inventors have also developed a closely matched anti-mouse CD40 mAb (closely matched to the anti-human CD40 mAb) which is useful to study the effects of anti-CD40 mAb therapy in a number of mouse models of immune and inflammatory disease. Development of anti-CD40 antibodies is complicated by the fact that CD40 is a potent signaling molecule. Antibodies that bind to this antigen can be categorized based on the ability to stimulate CD40 signaling as well as the ability to block the CD40/gp39 interaction.

Applicants' anti-human CD40 mAb, which blocks the CD40/gp39 interaction, was selected from an extensive panel of anti-CD40 mAbs. The antibody, labeled 2.220, was chimerized and humanized. "Chimeric" antibodies comprise a light chain and a heavy chain: the light chain is comprised of a light chain variable region and a light chain constant region; the heavy chain is comprised of a heavy chain variable region and a heavy chain constant region. Chimeric antibodies comprise variable regions from one species and constant regions from another species (for example, mouse variable regions joined to human constant regions). (See, e.g., U.S. Patents 4,816,397 and 4,816,567). Each of the light chain variable region (VL) and heavy chain variable region (VH) consists of "framework" regions interrupted by three hypervariable regions called "complementarity determining regions" or "CDRs". "Humanized" antibodies comprise antibodies with human framework regions combined with CDRs from a donor mouse or rat immunoglobulin. (See, e.g., U.S. Patent 5,530,101). Encompassed within the scope of the present invention are humanized antibodies which comprise CDRs derived from the murine variable chains disclosed herein.

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The most straightforward approach to humanizing an antibody consists of grafting the CDRs from the donor mAb onto a human framework (Jones, P.T., et al., (1986) *Nature* 321:522-525). However, certain framework residues support CDR structure, and contact antigen grafting murine CDRs onto human framework templates may diminish the binding activity of the resulting humanized mAb (Foote, J., et al., (1992) *J. Mol. Biol.* 224:487-499). Assessing the potential contribution of specific framework residues to antibody affinity poses two problems. First, for a particular mAb it is difficult to predict which framework residues serve a critical role in maintaining the affinity and specificity. Second, for framework positions that differ between the parent mAb and the human template it is difficult to predict whether the amino acid derived from the murine parent or the human template will yield a more active mAb. Consequently, antibody humanization methods that rely exclusively on structural predictions are not always successful.

The prior art contains a description of a general antibody engineering strategy that addresses the difficulty of maintaining antibody binding activity following humanization (Rosok, M. J., et al., (1996) J. Biol. Chem. 271:22611-22618). Potentially important framework residues that differ between the parent mAb and the human template are characterized in a single step by synthesizing and expressing a combinatorial antibody library that contains all possible combinations of parent and human template amino acids at the framework positions in question. Variants displaying the optimal framework structure are identified by screening and subsequently, optimal framework structure(s) are determined by DNA sequencing. Typically, sequencing multiple active clones reveals critical framework positions that require the expression of a particular amino acid. Conversely, the expression of a murine or human amino acid at a library framework position at an equivalent frequency in the active clones is consistent with a less important function for that particular framework position. Thus, a humanized version of the antibody that preserves the binding activity of the parent mAb is rapidly identified based on functional binding.

The processes of antibody humanization and affinity maturation are often performed in discreet steps (Rosok (1996), *supra*; Yelton, D. E., et al., (1995) J.

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Immunol. 155:1994-2004; Wu, H., et al., (1998) Proc. Natl. Acad. Sci. USA 95:6037-6042; Baca, M., et al., (1997) J. Biol. Chem. 272:10678-10684; Marks. J.D., et al., (1992) J. Biol. Chem. 267:16007-16010). Using a modified strategy described below, multiple humanized versions of the murine mAb 2.220 displaying affinities equivalent to or better than the chimeric Fab were generated.

Applicants' chimeric anti-CD40 antibody of the present invention is referred to herein as "chi220". Applicants' closely matched anti-mouse CD40 mAb is referred to herein as "7E1". Applicants' humanized anti-CD40 antibodies of the present invention are referred to herein as "F4" and "L3.17".

Two different isotype variants of 7E1 were generated. These two variants of 7E1 are useful in examining the role of the Fc portion of the molecule in anti-CD40 mAb therapy in preclinical models of immune and inflammatory diseases. The generation of the anti-mouse CD40 mAb, the criteria used to select one which matched the properties of chi220, the generation of the isotype variants of the mAb and their *in vivo* activity in mouse models of immune disease are also presented herein. Studies with both chi220 and its parent murine mAb 2.220 in monkeys, as well as studies with 7E1 in mice, showed that these anti-CD40 mAbs are potent immunosuppressive agents, and will be discussed in more detail below. The studies described herein were performed using standard technology known by those skilled in the art.

In summary, Applicants' antibodies have been shown to suppress a humoral immune response in monkeys. Likewise, two isotype variants of a closely matched anti-mouse CD40 mAb, 7E1, showed immunosuppressive activity in a number of preclinical models of human disease. Taken together, these findings indicate that chi220, F4 and L3.17 are useful for clinical application in the treatment of autoimmune diseases and transplantation.

The following examples are for illustrative purposes only and do not limit the scope of Applicants invention, which is defined only by the claims.

#### Example 1

Selection of Murine Anti-Human CD40 Antibody

# A. Isolation and In Vitro Characterization

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A panel of monoclonal antibodies was generated against human CD40 using standard hybridoma technology with human CD40 fusion protein as the immunogen. Antibodies were screened for binding to CD40 using both a CD40<sup>+</sup> cell line and fusion proteins. Assays of gp39 binding to CD40 and functional assays of stimulation through CD40 were used to characterize cloned antibodies. Selected antibodies were then characterized for crossreactivity with primate cells to assess the suitability of the antibodies for use in primate preclinical models.

# 1. Immunization and Fusion

Two fusions were performed to generate hybridomas producing anti-human CD40 mAbs. Immunizations to generate immune lymphocytes were carried out in 6-8 week old female BALB/c mice using as the immunogen a recombinant fusion protein consisting of the extracellular domain of human CD40 fused to the hinge, CH2 and CH3 domains of a murine IgG2b antibody (hCD40-mG2b).

For fusion 40-1, the mouse was initially immunized subcutaneously at 3-4 sites with an emulsion (total of 200 ul) of 30 ug hCD40-mG2b in complete Freund's adjuvant. The animal was similarly boosted on day 21 with hCD40-mG2b in incomplete Freund's adjuvant and then given a final pre-fusion immunization on day 37 by intravenous injection of 30 ug of hCD40-mG2b in PBS. Immunizations for fusion 40-2 were similarly performed except that Ribi adjuvant (R-730) was substituted for Freund's adjuvant. Booster immunizations were on days 21 and 42 with the final pre-fusion boost on day 58.

Three days following final booster injections, leukocytes from the spleen and lymph nodes were harvested and fused at a 3:1 ratio with X63-Ag8.653 mouse myeloma cells using standard methods (Kearney et al., <u>J. Immunol.</u> (1979) 123:1548-50; Lane, <u>J. Immunol.</u> (1985) 81:223-28). Cell suspensions from each fusion were seeded into ten 96-well cell culture plates at a plating density of approximately 170,000 total cells (pre-fusion) per well.

#### 2. Screening and Cloning

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Two assay formats were used to identify mAbs with specificity for native human CD40. Cell culture supernatants from all wells were initially screened for their ability to bind to a CD40 positive, EBV-transformed human B cell line (1A2-2C) in an ELISA-based format. Each supernatant was then tested in an ELISA based format for reactivity with a purified, recombinant fusion protein consisting of the extracellular domain of human CD40 fused to the hinge, CH2 and CH3 domains of a human IgG1 antibody, hCD40-Ig, and a similarly constructed irrelevant human Ig fusion protein, Leu8-hIg (Hollenbaugh, et al., EMBO J. (1992) 11:4313-4321). Reactivity with the former and not the latter fusion protein, coupled with the cell binding data, established the presence of antibody specific for native CD40 in approximately 200 master wells.

A key functional property for the desired anti-CD40 mAb was the capacity to completely block the interaction of CD40 and its ligand, gp39. Thus, as the next step in antibody selection, all CD40 specific master well supernatants were assessed for their ability to inhibit the binding of the soluble, recombinant murine CD8-human gp39 fusion protein, sgp39, to immobilized hCD40-Ig in an ELISA-based format. Those that completely inhibited this interaction were subsequently titrated in the same format to establish which wells contained the highest titer of inhibiting antibody. From this analysis, ten of the most strongly inhibiting master wells were selected for cloning.

Cloning of the appropriate antibody secreting cells was accomplished in a two step process. Cells from each master well were first "minicloned" at a seeding density of 10 cells/well after which the highest titered, CD40-specific "miniclone" well was formally cloned by a limiting dilution method.

#### 3. Further Characterization

Six assay formats were used to further characterize the antibodies. These were inhibition of sgp39 binding to human B cells, inhibition of B cell proliferation induced by sgp39 plus anti-IgM, inhibition of *in vitro* antibody synthesis by B cells induced by activated T cells, direct costimulation of B cells with anti-IgM, costimulation of B cells with anti-IgM in the presence of cross-linking anti-kappa

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light chain antibody, and costimulation of B cells with anti-IgM in the presence of a second anti-CD40 mAb, G28-5. This mAb was known to possess strong costimulatory activity and to incompletely block CD40/gp39 interaction. It has been included for comparison purposes in many of these assays.

This analysis led to the selection of four mAbs: 1.66 (IgG2b), 2.36 (IgG2a), 2.174 (IgG1) and 2.220 (IgG2a). Tests were run to characterize the mAbs. In one experiment, cells from the human B cell line Raji were incubated with 2 or 20 µg/ml of various anti-CD40 mAbs followed by a second incubation in undiluted COS cell supernatant containing mCD8-gp39 fusion protein (sgp39). Bound sgp39 was detected by further incubation of the cells with a FITC labeled anti-mCD8 mAb and analysis of the cells on a FACScan. Percent inhibition was calculated by dividing mean fluorescence of samples incubated with antibody by the mean fluorescence of samples without antibody in the first incubation (Figure 1).

As shown in Figure 1, each of these four mAbs was capable of completely inhibiting the binding of sgp39 fusion protein to a human B cell line expressing high levels of CD40, although in the case of 2.174, a relatively high concentration of antibody was required for complete blockade. Similar data were obtained using human tonsillar B cells. These data were paralleled by two functional assays. First, it was shown that each mAb was able to completely block sgp39-mediated costimulation of human tonsillar B cells. Second, each significantly inhibited the production of IgG and IgM in an *in vitro* T cell-dependent B cell antibody synthesis assay.

Three of the four antibodies showed limited ability to costimulate B cell proliferation in the presence of anti-IgM. MAb 2.220 was more consistent in its ability to induce weak costimulatory activity. With the addition of an anti-kappa light chain antibody, used to cross-link the anti-CD40 mAbs, 2.36 gained significant costimulatory activity, while the activity of other three antibodies was not affected. The costimulatory ability of G28-5 was shown to be differentially modulated when it was paired in combination with each of the four new anti-CD40 mAbs. MAbs 1.66 and especially 2.174 enhanced G28-5 costimulation, whereas 2.220 and 2.36 suppressed it.

Following selection based on evaluations in human *in vitro* systems, the four anti-CD40 mAbs were further examined for their suitability for *in vivo* evaluation in non-human primate studies. Two key points of analysis were the relative potency of each for binding to primate B cells and suppression of *in vitro*, T cell-dependent B cell antibody synthesis. It was found that all four mAbs crossreacted with cynomolgus macaque (*Macaca fascicularis*) B cells. 2.36 and 2.220 bound with higher avidity than 2.174 and 1.66. Lower apparent binding of mAbs 2.174 and 1.66 was not due to their particular isotypes, as other isotype-matched anti-CD40 mAbs demonstrated binding levels comparable to 2.36 and 2.220 (e.g., G28-5 and 2.118). These results were in contrast to that observed with human B cells where each of the mAbs demonstrated comparable binding. The ability of the four mAbs to suppress antibody synthesis by monkey B cells was found to parallel the ability to bind.

## B. In Vivo Characterization

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Two studies were performed in non-human primates using the murine anti-human CD40 mAbs to assess the suitability of anti-CD40 as an immunosuppressive agent and to select the appropriate antibody for further development. First, the *in vivo* clearance and acute toxicity of the four selected anti-CD40 mAbs were compared. These results were used to select two antibodies, 2.36 and 2.220, that were then tested in a second study designed to assess efficacy in the inhibition of the antibody response to a T-dependent antigen and acute toxicity.

Primate Efficacy Study with 2.36 and 2.220

Based upon previous findings, mAbs 2.36 and 2.220 were evaluated for their ability to suppress a T-dependent antibody response following intravenous administration to cynomolgus monkeys. This study was divided into three phases (Figure 2). In Phase I, four groups consisting of one or two male and two female cynomolgus monkeys each were immunized intravenously on day 1 with sheep red blood cells (SRBCs), and then treated with 20 mg/kg of mAb 2.36, 2.220, 1.106 (IgG1 murine anti-human gp39, positive control), or L6 (IgG2a murine anti-human tumor antigen, negative control) on days 1, 3, and 5. IgM and IgG titers to the SRBC immunogen, serum levels of test and control articles, the presence of anti-test and

control article antibodies, serum immunoglobulin levels, peripheral blood leukocyte counts, and the frequencies of various subpopulations of peripheral blood lymphocytes were determined. In phase II, after the control and test articles had cleared, the animals were immunized with SRBCs and a second antigen, keyhole limpet hemocyanin (KLH), to assess the induction of immunological tolerance and the reversibility of the observed immunosuppression. In phase III, selected animals were reimmunized to determine if the initially suppressed anti-SRBC antibody response recovered following an additional challenge with SRBCs and to assess the secondary antibody response to KLH.

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An experiment was performed to show that MAb 2.220 significantly suppressed the primary antibody response to SRBCs (Figure 3). Monkeys were treated with 20 mg/kg of either mAb 1.106, L6, 2.36 or 2.220 on Phase I Days 1, 3, and 5. Monkeys were immunized with SRBC on Day 1 of Phase I, II and III. Figure 3a shows the results of serum samples that were analyzed for IgM anti-SRBC antibodies; Figure 3b shows the results of serum samples that were analyzed for IgG anti-SRBC antibodies. Data are expressed as the geometric mean anti-SRBC titer for each group (n=3 or 4).

The peak primary response was inhibited 85% and 98% for IgM and IgG, respectively. Following clearance of mAb 2.220 in serum to below detectable levels, the peak secondary response to SRBCs was still inhibited 79% and 56% for IgM and IgG, respectively, compared to the negative control response in Phase I. This was in contrast to the positive control, mAb 1.106, with which a strong secondary antibody response to SRBCs was observed. The tertiary response to SRBCs was not inhibited, indicating that mAb 2.220 induced a prolonged immunosuppression, but not immunological tolerance. All animals immunized with KLH had a primary and secondary anti-KLH response, suggesting that the immunosuppression was reversible. Animals treated with 2.36 were not included in phase II because there was no significant inhibition seen in phase I of the study.

Mean peak serum concentrations, occurring immediately after the last dose, were 744 and 405  $\mu$ g/ml for mAbs 2.220 and 2.36, respectively. Whereas mAb 2.36

cleared from the serum to below detectable levels by day 15, mAb 2.220 did not clear until day 29. Both mAbs 2.36 and 2.220 were immunogenic.

There were no drug-related clinical observations, changes in body weight or food consumption, or alterations in hematology or serum Ig levels in any animal. The only drug-related findings observed were transient 70% and 43% decreases in the percentages of peripheral B cells with mAbs 2.36 and 2.220, respectively. Recovery of B cells to normal levels occurred within 2-3 weeks post-treatment.

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In summary, mAb 2.220 significantly suppressed the antibody response to SRBCs and 2.36 did not. Although mAb 2.220 induced a prolonged antigen-specific immunosuppression, it was reversible. Based on these findings, mAb 2.220 was selected for further development.

#### Example 2

Generation of Chimeric Antibody chi220

To address immunogenicity of the murine anti-human mAb 2.220, recombinant forms in which variable regions are fused to human constant regions were generated and compared for in vitro efficacy. The two approaches used were generation of a chimeric antibody, containing the unaltered murine variable regions, and humanized forms in which murine hypervariable regions (CDRs) are grafted on human framework sequences within the variable regions. Chimeric antibodies retain the antigen binding properties of parent antibody, but may have a greater likelihood of being immunogenic. Humanized antibodies are less likely to be immunogenic, but mutations introduced in the humanization can affect antigen binding.

A. Construction and *In Vitro* Characterization of Chimeric and Humanized Antibodies

The VL and VH regions from the anti-CD40 mAb 2.220 were obtained by PCR. cDNA was generated from RNA isolated from the hybridoma expressing the 2.220 mAb using an IgG1-specific or a Cκ-specific anti-sense primer to obtain the VH or VL regions, respectively. A poly-G tail was added to these single stranded cDNAs. The variable regions were then amplified by PCR using as a sense primer an oligonucleotide containing a poly-C sequence, complimentary to the poly-G tail, and a

nested set of antisense primers. The PCR product obtained was then inserted into a bacterial vector using restriction sites included in the primers. Multiple clones were then sequenced by dideoxynucleotide sequencing. Two independent experiments were performed, beginning at the RNA stage and the sequences obtained were the same.

To generate a chimeric form of the antibody, the variable regions were amplified by PCR using primers that introduced a sequence encoding the signal sequence of the human antibody found to most closely match the 2.220 sequence, as shown in Figure 4. The underlined portions of the light chain variable sequence (Figure 4a) and the heavy chain variable sequence (Figure 4b) designate the inserted signal sequences of the human antibody with the closest homology to murine 2.220. These PCR products were inserted into a vector containing sequences encoding the constant regions of human kappa or of human  $\gamma 1$  to generate complete light or heavy chain, respectively. The vectors also contained appropriate drug resistance genes for the generation and amplification of stable lines expressing the protein. Protein for initial characterization was produced by transient expression from COS cells followed by Protein A purification.

As an example, a chimeric antibody producing cell line was generated by cotransfecting CHO DG44 cells with separate expression vectors for the heavy and light chains of the chimeric antibody, and the high copy number electroporation method was used to promote co-integration. (See, U.S. Patent 4,956,288). The chi220 heavy and light chains were cloned into the pD17 and pD16 expression vectors, respectively. Both vectors are derived from the InVitrogen plasmid pcDNA3, and contain the following features (Figure 12): (1) the neomycin resistance gene from pcDNA3 was replaced with the murine dihydrofolate reductase (DHFR) gene under control of the enhancerless SV40 promoter (also referred to as the "weakened DHFR"; note that only the promoter was weakened, not the DHFR enzyme - the enhancerless promoter still contains the SV40 origin of replication, so these vectors can be used in transient COS transfections); (2) the gene of interest is expressed from the CMV promoter, and the poly adenylation signal is from the bovine growth hormone gene; (3) the expression cassette for the gene of interest is flanked by transcription termination

sequences (i.e., 5' to the promoter and 3' to the poly A site); (4) the vectors contain two distinct restriction site polylinkers, one 3' to the promoter for cloning the gene of interest, and one 5' to the promoter for vector linearization prior to transfection; and (5) the ampicillin resistance gene and ColE1 origin for plasmid propagation in E. coli.

The heavy and light chain genes used were genomic constructs, with the following modifications: (1) the coding sequences for the heavy chain signal peptide, variable region and CH1 domain were contiguous (i.e., contained no introns); and (2) the coding sequences for the light chain signal peptide and variable region were contiguous.

Other expression vectors known by those skilled in the art, and capable of expressing a chimeric antibody of the present invention, are contemplated by the present invention. A nucleic acid sequence useful in an expression vector capable of expressing a heavy chain of a chimeric antibody of the present invention is shown in Figure 13; a nucleic acid sequence useful in an expression vector capable of expressing a light chain of a chimeric antibody of the present invention is shown in Figure 14.

The complete amino acid sequence of the heavy and light chains of the chimeric antibody ("chi220"), including the variable and constant regions, is as follows (the bold amino acids indicate variable heavy and variable light):

20 Heavy Chain Sequence (SEQ ID NO:3)

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	QIQLVQSGPE	LKKPGETVRI	SCKASGYAFT	TTGMQWVQEM	PGKGLKWIGW	50
	INTHSGVPKY	VEDFKGRFAF	SLETSANTAY	LQISNLKNED	TATYFCVRSG	100
	NGNYDLAYFA	YWGQGTLVTV	<b>SA</b> ASTKGPSV	FPLAPSSKST	SGGTAALGCL	150
25	VKDYFPEPVT	VSWNSGALTS	GVHTFPAVLQ	SSGLYSLSSV	VTVPSSSLGT	200
	QTYICNVNHK	PSNTKVDKKV	EPKSCDKTHT	CPPCPAPELL	GGPSVFLFPP	250
	KPKDTLMISR	TPEVTCVVVD	VSHEDPEVKF	NWYVDGVEVH	NAKTKPREEQ	300
	YNSTYRVVSV	LTVLHQDWLN	GKEYKCKVSN	KALPAPIEKT	ISKAKGQPRE	350
	PQVYTLPPSR	DELTKNQVSL	TCLVKGFYPS	DIAVEWESNG	QPENNYKTTP	400
30	PVLDSDGSFF	LYSKLTVDKS	RWQQGNVFSC	SVMHEALHNH	YTQKSLSLSP	450
	GK					452

Light Chain Sequence (SEQ ID NO:4)

35 **DIVLTQSPAT LSVTPGDRVS LSCRASQSIS DYLHWYQQKS HESPRLLIKY** 50 **ASHSISGIPS RFSGSGSGD FTLSINSVEP EDVGIYYCQH GHSFPWTFGG** 100 **GTKLEIKR**TV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150

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DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200 LSSPVTKSFN RGEC 214

Several humanized forms of 220 were generated. This process involves the identification of murine and human germline sequences with the closest homology to the VH and VL domains. The murine germline sequences were used to identify likely locations of somatic mutations that have arisen during the process of affinity maturation. The human sequences were then used as template and regions of the sequence known or suspected to be important to the binding specificity are replaced in the human sequences for both VH and VL. The structures of these sequences were then modeled using as a template the protein with the closest homology for which a crystal structure has been solved. Plasmids encoding the humanized forms were generated using PCR directed mutagenesis and used to generate antibody by transient expression from COS cells. In vitro assays were performed with the chimeric and humanized antibodies of the present invention, and results are depicted in Figure 5. Figure 5a shows the results of a binding assay testing the binding of chi220 and h220v3 to hCD40-mG2b in an ELISA based assay. Wells of Immulon-2 plates were coated with hCD40-mG2b at a concentration of 10 ng/ml in PBS for 2 hrs. Wells were blocked with Specimen Diluent (Genetic Systems), and antibodies were added at the indicated concentrations. Following a 1hr incubation, wells were washed, and the presence of the antibody detected using peroxidase-conjugated goat anti-human IgG antibody. H220v3 is a humanized form of mAb 2.220. Values are the average of duplicate wells and error bars represent the standard deviation.

Figure 5b shows the results of an assay testing the inhibition of sgp39-mediated costimulation of human B cells with anti-human CD40 mAbs. Resting human tonsillar B cells (50,000/well) were incubated with sgp39 fusion protein, 20 µg/ml rabbit anti-human IgM coated immunobeads and the indicated concentrations of the anti-CD40 mAbs or medium only control in 96 well plates. 72 hrs after initiation of cultures, all wells were pulsed with 1 uCi/well [³H]thymidine and the cells cultured for an additional 18 hrs. Cells were then harvested and incorporated [³H]thymidine measured in a scintillation counter.

Based upon the results of *in vitro* assays (Figures 5a and 5b, that show both the chimeric and humanized antibody effectively bound CD40 and inhibited B cell stimulation) the chimeric antibody was chosen for further study.

#### Example 3

Efficacy of chi220

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A. Chimeric mAb 2.220: Single-Dose Efficacy Study in Nonhuman Primates Chi220 was evaluated in cynomolgus monkeys for its ability to suppress primary and secondary humoral immune responses to T cell-dependent antigens. In one study, groups of four monkeys were immunized with sheep erythrocytes (SRBCs) and given a secondary immunization of ovalbumin (OVA) immediately prior to receiving a single intravenous bolus dose of either chi220 at 10, 40, or 100 mg/kg or sterile phosphate buffered saline (PBS) as a control. Substantial suppression of the primary humoral immune response against SRBCs was observed at all three dose levels, demonstrating efficacy of chi220 in primates. A dose-dependent transient depletion of peripheral blood B cells was observed in all of the chi220-treated monkeys, with the time to recovery also being dose dependent. At the two highest doses, transient mild decreases in the group mean absolute numbers of peripheral blood T cells were observed. Transient minimal decreases in serum IgM levels were observed, with no drug related changes in serum levels of IgG or IgA.

To assess the induction of immunological tolerance and reversibility of immunosuppressive activity, all monkeys were immunized with OVA, SRBCs, and a neoantigen, keyhole limpet hemocyanin (KLH) on day 149, when serum levels of chi220 in the 100 mg/kg group were below levels believed to be immunosuppressive (~10 µg/ml) and the numbers of peripheral blood B cells had returned to predose levels. The anti-SRBC response at the lowest dose level was generally comparable to the primary anti-SRBC antibody response in the control monkeys. However, the antibody response to SRBCs was still partially or substantially suppressed in the monkeys treated at the two higher dose levels.

To further explore the dose dependence of immunosuppression and B cell depletion, a second study was performed in which additional monkeys (four/group) were immunized with SRBCs, and then given a single dose of chi220 at 0.1 or 1.0

mg/kg or PBS. Suboptimal immunosuppression of the antibody response to SRBCs was observed at both dose levels. Moderate depletion of peripheral blood B cells was evident in monkeys that received 1.0 mg/kg chi220 by Day 8, reversing by Day 29. At 0.1 mg/kg, a decrease in the mean number and percentage of peripheral blood B cells was observed, but values were not outside the normal historical ranges for percent B cells. Historical limits have not been established for absolute numbers of peripheral blood B cells. Transient minimal decreases in peripheral blood T cell numbers and mild decreases in *ex vivo* T cell proliferation were observed in monkeys that received 1 mg/kg chi220. Finally, there was no evidence of complement activation or drug-related changes in the serum levels of IL-6 or TNFα. *Ex vivo* T cell activation, complement activation, and serum cytokine levels were not assessed in monkeys treated with 10, 40, or 100 mg/kg chi220.

In both studies, serum samples were examined following chi220 administration for circulating levels of test article, and to assess antibody formation against the test article. Pharmacokinetic analysis indicated that the mean peak serum concentration (Cmax) of chi220 did not increase in a manner proportional to the dose increment, and that the half-life of chi220 became prolonged as the dose administered was increased. Chi220 was found to be immunogenic when administered at 0.1, 1 or 10 mg/kg. At circulating concentrations above 10 µg/ml, it appears that chi220 can suppress the antibody response directed against it.

### 1. Experimental Protocol

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In the initial study mentioned above, cynomolgus monkeys were assigned to four groups consisting of two males and two females each. All monkeys were immunized 28 days prior to chi220 or control article administration with OVA (5 mg/kg, im and 10 mg/kg, sc). On Day 1, all monkeys were immunized with SRBCs (1.7 ml/kg of a 10% suspension, iv) and given a secondary immunization of OVA (5 mg/kg, im and 10 mg/kg, sc) immediately prior to receiving a single intravenous bolus dose of either chi220 at 10, 40, or 100 mg/kg or sterile PBS as a control. On Day 149, after the serum levels of chi220 had fallen below putatively immunosuppressive levels ( $\sim$ 10  $\mu$ g/ml) and the levels of peripheral blood B cells had returned to predose levels in all groups, the monkeys were immunized with OVA, SRBCs, and KLH (10

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mg/animal, im). The purpose of the KLH immunization was to show that the monkeys were able to mount an immune response to a neoantigen after being treated with chi220.

In order to demonstrate a better dose response with respect to immunosuppression and peripheral blood B cell depletion, additional monkeys in a second study (two/sex/group) were immunized with SRBCs, and then given a single dose of either chi220 at 0.1 or 1.0 mg/kg or PBS as a control on Day 1. Hematological parameters and peripheral blood lymphocyte subpopulations were monitored at selected time points during both studies. Serum chemistry parameters were monitored in monkeys that received 10, 40, or 100 mg/kg chi220, but were not monitored at the 0.1 and 1 mg/kg dose levels because no drug-related findings were observed at the higher doses. In addition, serum levels of IgM, IgG, IgA, and chi220 were measured. To assess efficacy, specific IgM and IgG antibody formation against the SRBC and OVA immunogens was determined on the appropriate serum samples obtained just prior to immunogen administration and weekly thereafter. Specific IgM and IgG antibody formation against the test article for monkeys that received chi220 was determined prior to test article administration on Day 1, and weekly thereafter. Geometric mean titers were used when comparing antibody responses between groups. In addition, total hemolytic complement activity (CH<sub>50</sub>) and C4d fragment levels were measured, and TNF- $\alpha$  and IL-6 levels were determined in monkeys that received 0.1 or 1 mg/kg chi220 at selected time points following chi220 administration. Ex vivo peripheral blood T cell activation was also assessed following stimulation with concanavalin A in monkeys receiving 0.1 and 1 mg/kg chi220 on Days 17 and 31 to assess the effects of chi220 on T cell responsiveness to a mitogen. Finally, all monkeys were observed daily for clinical signs of toxicity, body weights recorded weekly, and food consumption monitored daily.

Monkeys were immunized with SRBC prior to receiving vehicle or 10, 40, or 100 mg/kg chi220 (Figure 6a) or 0.1 or 1 mg/kg chi220 (Figure 6b) on Day 1. Serum samples were analyzed for IgM anti-SRBC antibodies by ELISA. Data are expressed as the geometric mean anti-SRBC antibody end-point titer (EPT) for each group (n=2 [100 mg/kg group beyond Day 15] or 4), where EPT is equivalent to the reciprocal of

the greatest dilution of serum with an absorbance of greater than two times the mean plate background.

#### 2. Results

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# a. Anti-SRBC Antibody Response

When administered to monkeys at 10, 40, or 100 mg/kg, chi220 was effective at substantially suppressing the primary antibody response against SRBCs. On the peak day of the control primary IgM anti-SRBC antibody response (Day 8), the mean primary IgM anti-SRBC antibody response was suppressed approximately 92-94% in the monkeys treated with 10, 40, and 100 mg/kg chi220, compared to controls (Figure 6a). The group mean IgM anti-SRBC antibody response did not become positive through Day 85 at the 10, 40 or 100 mg/kg dose levels. On the peak day of the control primary IgG anti-SRBC antibody response (Day 15), the mean primary IgG anti-SRBC antibody response was suppressed 98%, 99%, and 85% in monkeys that received 10, 40, and 100 mg/kg, respectively, compared to controls (Figure 7a). Higher overall predose anti-SRBC antibody titers in the 100 mg/kg group may have accounted for the apparent lack of dose-dependent immunosuppression. Overall, monkeys treated with 10 or 100 mg/kg chi220 did not mount a primary IgG anti-SRBC antibody response through Day 85. However, two of the monkeys treated with 40 mg/kg chi220 had a delayed primary IgG antibody response to SRBCs (comparable to the control response in magnitude), which became positive by Day 36 and peaked on Day 51.

On Day 149, after the serum levels of chi220 had fallen below putatively immunosuppressive levels (~10 µg/ml) and the levels of peripheral blood B cells had returned to predose levels in all groups, the monkeys were immunized a second time with SRBCs. As expected, control monkeys mounted a strong secondary IgG antibody response to SRBCs. Monkeys treated with 10 mg/kg chi220 mounted primary IgM and IgG antibody responses to SRBCs that were generally comparable to the primary antibody response in the control monkeys. However, the antibody response to SRBCs was still partially suppressed at the 40 mg/kg dose level and substantially suppressed at the 100 mg/kg dose level. Although two monkeys treated with 40 mg/kg chi220 that had previously mounted weak primary antibody responses

to SRBCs developed IgM and IgG anti-SRBC antibody titers characteristic of a secondary antibody response, the anti-SRBC antibody responses in the two other monkeys in that group and the remaining monkeys treated with 100 mg/kg chi220 was still approximately 90% suppressed compared to the mean primary anti-SRBC antibody response of the control monkeys.

Suboptimal immunosuppression of the antibody response to SRBCs was observed following administration of 0.1 or 1.0 mg/kg chi220 (Figures 6b and 7b). While all of the chi220-treated monkeys mounted a positive IgM antibody response to the SRBC antigen, the overall mean peak IgM anti-SRBC antibody response was suppressed approximately 56% in the monkeys treated with 1 mg/kg chi220 compared to the mean peak control response. No suppression of the IgM anti-SRBC antibody response was observed in monkeys treated with 0.1 mg/kg chi220. The mean IgM anti-SRBC antibody response peaked on Day 15 in the control monkeys, and on Day 8 in the monkeys that received 0.1 and 1.0 mg/kg chi220. Overall, the mean peak IgG anti-SRBC antibody response was suppressed 56% and 42% in the monkeys treated with 0.1 and 1.0 mg/kg chi220, respectively. The mean IgG anti-SRBC antibody response peaked on Day 15 in the control monkeys and monkeys treated with 1 mg/kg chi220, and on Day 8 in the monkeys that received 0.1 mg/kg chi220.

# b. Anti-OVA Antibody Response

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Monkeys were administered an intravenous dose of 10, 40, or 100 mg/kg chi220 on Day 1. In addition all monkeys were immunized with OVA on Days -28, 1, and 149. Serum samples were analyzed for IgM (Figure 8a) or IgG (Figure 8b) anti-OVA antibodies. Data are expressed as the geometric mean anti-OVA endpoint titer (EPT) for each group (n=2 [100 mg/kg group beyond Day 15] or 4), where EPTs are equivalent to the reciprocal of the greatest dilution of serum with an absorbance of greater than two times the mean plate background.

Specific IgM and IgG antibody formation against OVA was monitored weekly during the study in monkeys that received 10, 40, or 100 mg/kg chi220. The primary and secondary anti-OVA antibody responses were highly variable and generally weak in all monkeys (Figure 8). Monkeys scheduled to receive chi220 on Day 1 had greater anti-OVA antibody titers than monkeys in the control group.

On Day 149, the monkeys were given a tertiary OVA immunization. All of the monkeys mounted positive IgG antibody responses to OVA within 7 days following challenge. Control monkeys and monkeys treated with 10 mg/kg chi220 had antibody titers characteristic of a tertiary antibody response, whereas monkeys treated with either 40 or 100 mg/kg chi220 developed antibody titers that were more characteristic of a secondary antibody response.

#### c. Anti-KLH Antibody Response

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Monkeys were administered an intravenous dose of 10, 40, or 100 mg/kg chi220 on Day 1. In addition, all monkeys were immunized with KLH on Day 149. Serum samples were analyzed for IgM (Figure 9a) or IgG (Figure 9b) anti-KLH antibodies. Data are expressed as the geometric mean anti-KLH endpoint titer (EPT) for each group (n=2 [100 mg/kg group beyond Day 15] or 4), where EPTs are equivalent to the reciprocal of the greatest dilution of serum with an absorbance of greater than two times the mean plate background.

On Day 149, after the serum levels of chi220 had fallen below putatively immunosuppressive levels ( $\sim$ 10  $\mu$ g/ml) and the levels of peripheral blood B cells had returned to predose levels in all groups, the monkeys were immunized with KLH (10 mg/animal, im). All monkeys mounted positive IgM and IgG antibody responses to KLH, demonstrating that the ability to respond to a new antigen was not compromised (Figure 9).

d. Serum Levels of Test Article and Anti-Test Article Antibody Response Serum samples were examined following chi220 administration to determine circulating levels of test article and to assess antibody formation against the test article. The mean peak serum concentration (Cmax) of chi220 occurred three minutes following the administration of 10 or 40 mg/kg doses and six hours following administration of the 100 mg/kg dose. Cmax values of chi220 were 329, 2429, and 2343 µg/ml in the monkeys treated with 10, 40, or 100 mg/kg chi220, respectively. There was, however, considerable variation in the Cmax of individual monkeys in the 40 and 100 mg/kg groups. The mean serum half-life of chi220 was estimated to be approximately 114, 173 and 315 hours in monkeys treated with 10, 40, or 100 mg/kg chi220, respectively.

Mean Cmax values, occurring three minutes following chi220 administration, were 1.77 and 33  $\mu$ g/ml for 0.1 and 1 mg/kg doses, respectively. No gender related differences in the serum levels of chi220 were observed within each dose level. Mean AUC<sub>inf</sub> values were 15.5 and 847 ug.h/ml, for 0.1 and 1 mg/kg doses, respectively.

Taken together, the studies suggest that the half-life of chi220 becomes prolonged as the dose administered is increased. Furthermore, it appears that the Cmax of chi220 increases in a manner disproportionate to the dose increment.

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Although the IgM anti-test article response was minimal or absent in the monkeys that received 10, 40, or 100 mg/kg chi220, a significant IgG anti-test article antibody response was observed in the monkeys that received 10 mg/kg chi220. The mean IgG anti-test article antibody response in the monkeys that received 10 mg/kg chi220 became positive on Day 29, approximately 1 week after the mean group serum concentration of chi220 had fallen below  $10~\mu$ g/ml, and peaked on Days 36 and 43 at a geometric mean titer of 12,627. The appearance of IgG anti-test article antibodies in the monkeys that were treated with 10 mg/kg chi220 also coincided with the first detectable increases in B cell numbers following depletion. By the last day measured (Day 149), the monkeys that received 40 or 100 mg/kg chi220 had still not mounted a positive antibody response against chi220, although the group mean chi220 serum levels were below 10  $\mu$ g/ml by Day 57 (40 mg/kg group) or Day 92 (100 mg/kg group).

Chi220 was immunogenic when administered at 0.1 or 1 mg/kg. Three of four monkeys that received either 0.1 or 1 mg/kg chi220 had weakly positive IgM anti-test article antibody responses by Day 15 during the study. Three of four monkeys treated with 1 mg/kg chi220 had significant IgG anti-test article antibody responses by Day 22, peaking at a geometric mean endpoint titer of 16,618. Overall, the geometric mean IgG anti-test article antibody response was not positive in the monkeys that received 0.1 mg/kg chi220, and only one monkey that received 0.1 mg/kg chi220 had a weakly positive IgG anti-test article antibody response, peaking at an endpoint titer of 2430 on Day 22. Collectively, these data suggest that chi220 is capable of immunosuppressing an antibody response against itself at serum levels of greater than approximately 10 µg/ml.

### Example 4

Generation of Humanized Anti-CD40 Antibodies F4 and L3.17

A variety of methods known in the art have been used for the humanization of mAbs. Structure-based approaches have proven useful but the complexity that arises from the large number of framework residues potentially involved in binding activity diminishes the rate of success. Rather than predicting the optimal framework based on modeling, the antibody library approach described below permits identification of active framework conformations based on screening numerous combinations. Mutagenesis approaches coupled to selection methods permit the analysis of many 10 variants and mimics the in vivo maturation process (reviewed in Marks, J.D., et al., (1992) J. Biol. Chem. 267:16007-16010). Codon-based mutagenesis permits the construction of libraries that characterize the contribution of specific residues and thus, is more efficient than random mutagenesis approaches. For example, errorprone PCR can not be used to synthesize the combinatorial framework libraries described below. Moreover, random mutagenesis creates larger more diverse libraries and unfortunately, the majority of mutations do not enhance the binding activity of the mAb. Consequently, larger numbers of clones must be screened to identify active variants.

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A strategy termed "guided selection" has been used to isolate human mAbs from a phage display library in a two-step process that uses a rodent mAb as a template (Jespers, L. S., et al., (1994) Bio/Technology 12:899-903). Recently, a variation of guided selection using phage display technologies was described in which a chimeric Fd fragment was used to select a L chain from a library containing human L chains with grafted murine CDR3 (Rader, C., et al., (1998) Proc. Natl. Acad. Sci. USA 95:8910-8915). Subsequently, the most active L chain was used to select an H chain from a human H chain library containing the murine HCDR3. The mAbs isolated by these approaches are entirely human (Jespers, supra) or mostly human (Rader, supra), but the large antibody diversity introduced at each step of the processes necessitates the use of affinity enrichment methods.

The following materials and methods were utilized to generate the humanized anti-CD40 antibodies F4 and L3.17 of the present invention.

# 1. Construction of Chimeric anti-CD40

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Based on the sequence of anti-CD40 murine mAb 2.220 overlapping oligonucleotides encoding VH and VL (69-75 bases in length) were synthesized and purified. The variable H and L domains were synthesized separately by combining 25 pmol of each of the overlapping oligonucleotides with Pfu DNA polymerase (Stratagene) in a 50 µl PCR reaction consisting of 5 cycles of: denaturing at 94°C for 20 sec, annealing at 50°C for 30 sec, ramping to 72°C over 1 min, and maintaining at 72°C for 30 sec. Subsequently, the annealing temperature was increased to 55°C for 25 cycles. A reverse primer and a biotinylated forward primer were used to further amplify 1  $\mu$ l of the fusion product in a 100  $\mu$ l PCR reaction using the same program. The products were purified by agarose gel electrophoresis, electroeluted, and phosphorylated by T4 polynucleotide kinase (Boehringer Mannheim) and were then incubated with streptavidin magnetic beads (Boehringer Mannheim) in 5 mM Tris-Cl, pH 7.5, 0.5 mM EDTA, 1 M NaCl, and 0.05% Tween 20 for 15 min at 25°C. The beads were washed and the non-biotinylated, minus strand DNA was eluted by incubating with 0.15 M NaOH at 25°C for 10 min. Chimeric anti-CD40 Fab was synthesized in a modified M13IX104 vector (Kristensson, K., et al., (1995) Vaccines 95, pp. 39-43, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY), termed M13IX104CS, by hybridization mutagenesis (Rosok, M. J., et al., (1996) J. Biol. Chem. 271:22611-22618; Kunkel, T.A. (1985) Proc. Natl. Acad. Sci. USA 82:488-492) using the V<sub>H</sub> and V<sub>L</sub> oligonucleotides in 3-fold molar excess of the uridinylated vector template. The M13IX104 vector was modified by replacing cysteine residues at the end of the kappa and  $\gamma 1$  constant regions with serine. The reaction was electroporated into DH10B cells and titered onto a lawn of XL-1 Blue.

Construction of Combinatorial Framework and Framework/CDR3
 Libraries.

The combinatorial framework library (Hu I) was synthesized by the same method used to construct the chimeric anti-CD40, with modifications. Overlapping

oligonucleotides encoding the framework regions of the H and L variable domains of the human template and the murine anti-CD40 CDRs as defined by Kabat *et al.* (Kabat, E.A., et al., (1991) Sequences of proteins of immunological interest (5th Ed), Washington DC: United States Department of Health and Human Services; Kabat, E.A., et al., (1977) *J. Biol. Chem.* 252:6609-6616) were synthesized. Degenerate oligonucleotides encoding both the murine and the human amino acids at seven VH and one VK framework position were synthesized (Figure 15, residues marked with asterisk).

The framework/HCDR3 (Hu II) and framework/HCDR3/LCDR3 (Hu III) libraries were synthesized by the same method as the combinatorial framework library, with modifications. The CDR residues selected for mutagenesis were: Ser<sup>95</sup>-Tyr<sup>102</sup> in HCDR3 and Gln<sup>89</sup>-Thr<sup>97</sup> in LCDR3 (Figure 15, underlined). Oligonucleotides encoding HCDR3 and LCDR3 were designed to mutate a single CDR residue and were synthesized by introducing NN(G/T) at each position as described in the art (Glaser, S. M., et al., (1992) *J. Immunol.* 149:3903-3913). The overlapping oligonucleotides encoding the framework library and non-library murine CDRs were combined with 25 pmol of the oligonucleotides encoding mutated HCDR3 or with 25 pmol each of the oligonucleotides encoding mutated HCDR3 and LCDR3.

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#### 3. Screening of Phage Expression Libraries

The Hu II and Hu III libraries were initially screened by a modified plaque lift approach known in the art, termed capture lift (Watkins, J. D., et al., (1998) *Anal. Biochem.* 256:169-177). Briefly, nitrocellulose filters (82-mm) were coated with goat anti-human kappa, blocked with 1% BSA, and were applied to an agar plate containing the phage-infected bacterial lawn. In the initial screen, phage were plated at 10<sup>5</sup> phage/100-mm plate. After the capture of phage-expressed anti-CD40 variant Fabs, the filters were incubated 3 h at 25°C with 5 ng/ml CD40-Ig in PBS containing 1% BSA. The filters were rinsed four times with PBS containing 0.1% Tween 20 and were incubated with goat anti-mouse IgG2b-alkaline phosphatase conjugate (Southern

Biotechnology) diluted 3000-fold in PBS containing 1% BSA for 1 h at 25°C. The filters were washed four times with PBS containing 0.1% Tween 20 and were developed as described (Watkins (1998), *supra*). To isolate individual clones, positive plaques from the initial screen were picked, replated at lower density (<10<sup>3</sup> phage/100-mm plate), and were screened by the same approach.

The Hu I combinatorial library was first screened by an ELISA that permits the rapid assessment of the relative affinities of the variants (Watkins, J. D., et al., (1997) *Anal. Biochem.* 253:37-45). In addition, the ELISA was used to characterize clones identified by capture lift screening. Briefly, microtiter plates were coated with 5 μg/ml goat anti-human kappa (Southern Biotechnology) and blocked with 3% BSA in PBS. Next, 50 μl Fab from the *Escherichia coli* culture supernatant or from the cell lysate, was incubated with the plate 1 h at 25°C, the plate was washed three times with PBS containing 0.1% Tween 20, and 0.1 μg/ml CD40-Ig in PBS containing 1% BSA for 2 h at 25°C. The plate was washed three times with PBS containing 0.1% Tween 20 and goat anti-mouse IgG2b-alkaline phosphatase conjugate diluted 3000-fold in PBS containing 1% BSA was added for 1 h at 25°C. The plate was washed three times with PBS containing 0.1% Tween 20 and was developed as described in the art (Watkins (1997), *supra*).

#### 4. DNA Sequencing

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Single-stranded DNA was isolated and the H and L chain variable region genes of the humanized antibodies of the present invention were sequenced by the fluorescent dideoxynucleotide termination method (Perkin-Elmer, Foster City, CA).

The nucleic acid (SEQ ID NO:7) and amino acid (SEQ ID NO:8) sequence of the variable light chain of humanized antibody F4 is as follows:

GAA ATT GTG TTG ACA CAG TCT CCA GCC ACC CTG TCT TTG TCT 42 Ε Ι V  $_{\rm L}$ Т Q S Ρ Α L S  $\mathbf{L}$ S 14 CCA GGG GAA AGA GCC ACC CTC TCC TGC AGG GCC AGT CAG AGT 84 30 G Ε R Α T L S C R Α Q 28 ATT AGC GAT TAC TTA CAT TGG TAC CAA CAG AAA CCT GGC CAG 126 Ι S Y D L Η W Υ 0 K 35 GCT CCC AGG CTC CTC ATC TAT TAC GCA TCC CAC TCC ATC TCT 168

	А	P	R	L	L	I	Y	Y	A	S	Н	S	I	S	56
5	GGC G	ATC I	CCA P	GCC A	AGG R	TTC F	AGT S	GGC G	AGT S	GGG G	TCT S	GGG G	ACA T	GAC D	210 70
	TTC F	ACT T	CTC L	ACC T	ATC I	AGC S	AGC S	CTA L	GAG E	CCT P	GAA E	GAT D	TTT F	GCA A	252 84
10	GTT	TAT	TAC	TGT	CAG	CAT	GGC	CAC	TCT	TTT	CCT	TGG	ACC	TTC	294
	V	Y	Y	C	Q	H	G	H	S	F	P	W	T	F	98
	GGA G	GGG G	GGG G	ACC T	AAG K	GTG V	GAA E	ATT I	AAA K						321 107
15	The nucleic acid (SEQ ID NO:9) and amino acid (SEQ ID NO:10) sequence of												e of		
	the variable heavy chain of humanized antibodies F4 and L3.17 is as follows:														
	CAG	GTG	CAG	CTG	GTG	CAA	TCT	GGG	TCT	GAG	TTG	AAG	AAG	CCT	42
	Q	V	Q	L	V	Q	S	G	S	E	L	K	K	P	14
20	GGG	GCC	TCA	GTG	AAG	GTT	TCC	TGC	AAG	GCT	TCT	GGA	TAC	GCC	84
	G	A	S	V	K	V	S	C	K	A	S	G	Y	A	28
25	TTC	ACT	ACC	ACT	GGC	ATG	CAG	TGG	GTG	CGA	CAG	GCC	CCT	GGA	126
	F	T	T	T	G	M	Q	W	V	R	Q	A	P	G	42
	CAA	GGG	CTT	GAG	TGG	ATG	GGA	TGG	ATC	AAC	ACC	CAC	AGC	GGG	168
	Q	G	L	E	W	M	G	W	I	N	T	H	S	G	56
30	GTC	CCA	AAG	TAT	GTC	GAG	GAC	TTC	AAA	GGA	CGG	TTT	GTC	TTC	210
	V	P	K	Y	V	E	D	F	K	G	R	F	V	F	70
	TCC	TTG	GAC	ACC	TCT	GTC	AGC	ACG	GCA	TAT	CTG	CAG	ATC	AGC	252
	S	L	D	T	S	V	S	T	A	Y	L	Q	I	S	84
35	AGC	CTA	AAG	GCT	GAG	GAC	ACT	GCC	GTG	TAT	TAC	TGT	GCG	AGA	294
	S	L	K	A	E	D	T	A	V	Y	Y	C	A	R	98
40	TCT	GGC	AAT	GGG	AAC	TAT	GAC	CTG	GCA	TAC	TTT	AAG	TAT	TGG	336
	S	G	N	G	N	Y	D	L	A	Y	F	K	Y	W	112
	GGC G	CAG Q	GGA G	ACC T	CTG L	GTC V	ACC T	GTC V	TCC S	TCA S					366 122
	The nucleic acid (SEQ ID NO:11) and amino acid (SEQ ID NO:12) sequence												ce		
45	of the variable light chain of humanized antibody L3.17 is as follows:														
	GAA	ATT	GTG	TTG	ACA	CAG	TCT	CCA	GCC	ACC	CTG	TCT	TTG	TCT	42
	E	I	V	L	T	Q	S	P	A	T	L	S	L	S	14
50	CCA	GGG	GAA	AGA	GCC	ACC	CTC	TCC	TGC	AGG	GCC	AGT	CAG	AGT	84
	P	G	E	R	A	T	L	S	C	R	A	S	Q	S	28

ATT AGC GAT TAC TTA CAT TGG TAC CAA CAG AAA CCT GGC CAG 126 Ι S D Υ W Y Q Q K Ρ G Q 42 5 GCT CCC AGG CTC CTC ATC TAT TAC GCA TCC CAC TCC ATC TCT R L  $_{\rm L}$ Ι Y Y Α S Η S Ι 56 GGC ATC CCA GCC AGG TTC AGT GGC AGT GGG TCT GGG ACA GAC Α R F S G S G S G Т 10 TTC ACT CTC ACC ACT AGC AGC CTA GAG CCT GAA GAT TTTGCA 252 T  $_{\rm L}$ T Ι S S  $\mathbf{L}$ Ε Ρ  $\mathbf{E}$ D 84 TATTAC TGT CAG CAT GGC CAC TCT TAT CCTTGG ACC TTC 294 15 Y Y C Q Η G Η S Y Р T 98 GGA GGG GGG ACC AAG GTG GAA ATT AAA 321 G G Τ K V Ε 107

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# 5. Expression and Purification of Fab

Certain Fabs were cloned into an expression vector under the control of the arabinose-regulated BAD promoter. In addition, a six-histidine tag was fused to the carboxyl-terminus of the H chain to permit purification with nickel-chelating resins. Purified Fab was quantitated as described (Watkins (1997), *supra*).

# 6. Characterization Assays

Immulon II microtiter plates were coated with 0.1 µg/ml CD40-Ig in PBS for 16 h at 4°C and were blocked with 3% BSA in PBS. The plates were washed three times in PBS containing 0.1% Tween 20 and Fab released from periplasmic space was diluted serially three-fold in PBS containing 1% BSA and incubated with the plate 2 h at 25°C. Subsequently, the plate was washed four times with PBS containing 0.1% Tween 20 and binding of antibody was detected by incubating with goat anti-human kappa-alkaline phosphatase conjugate diluted 2000-fold in PBS containing 1% BSA for 1 h at 25° C. The plate was washed four times with PBS containing 0.1% Tween 20 and was developed colorimetrically (Watkins (1997), *supra*).

To test the variants for inhibition of ligand binding, Immulon II microtiter plates were coated with 2 µg/ml anti-murine CD8 to capture sgp39 fusion protein which expresses the CD8 domain. The plates were rinsed once with PBS containing 0.05% Tween 20, and were blocked with 3% BSA in PBS. The plate was washed

once with PBS containing 0.05% Tween 20 and was incubated with cell culture media containing saturating levels of sgp39 for 2 h at 25°C. Unbound sgp39 was aspirated and the plate was washed two times with PBS containing 0.05% Tween 20. Next, 25 μl of purified variant Fabs diluted serially 3-fold in PBS was added followed by 25 μl of 4 μg/ml CD40-human Ig in PBS. The plates were incubated 2 h at 25°C and were washed three times with PBS containing 0.05% Tween 20. Bound CD40-Ig was detected following a 1 h incubation at 25°C with goat F(ab')2 anti-human IgG Fcγ-specific horseradish peroxidase conjugate (Jackson) diluted 10,000-fold in PBS. The plate was washed four times with PBS containing 0.05% Tween 20 and binding was quantitated colorimetrically by incubating with 1 mg/ml *o*-phenylenediamine dihydrochloride and 0.003% hydrogen peroxide in 50 mM citric acid, 100 mM Na<sub>2</sub>HPO<sub>4</sub>, pH 5. The reaction was terminated by the addition of H<sub>2</sub>SO<sub>4</sub> to a final concentration of 0.36 M and the absorbance at 490 nm was determined.

## 7. BIAcore Analysis

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The kinetic constants for the interaction between CD40 and the anti-CD40 variants were determined by surface plasmon resonance (BIAcore). CD40-Ig fusion protein was immobilized to a (1-ethyl-3-[3-dimethylaminopropyl]-carbodiimide hydrochloride) and N-hydroxysuccinimide-activated sensor chip CM5 by injecting 8  $\mu$ l of 10  $\mu$ g/ml CD40-Ig in 10 mM sodium acetate, pH 4. CD40-Ig was immobilized at a low density (~150 RU) to prevent rebinding of Fabs during the dissociation phase. To obtain association rate constants (k0n), the binding rate at six different Fab concentrations ranging from 25-600 nM in PBS was determined at a flow rate of 20  $\mu$ l/min. Dissociation rate constants (k0ff) were the average of six measurements obtained by analyzing the dissociation phase. Sensorgrams were analyzed with the BIAevaluation 3.0 program. Kd was calculated from Kd = k0ff/k0n. Residual Fab was removed after each measurement by prolonged dissociation.

The results of kinetics analysis for the humanized antibodies F4 and L3.17 compared to a chimeric Fab are shown in Table 1 below:

Table 1

Clone ID#	kon	Koff	$K_d$	Comment
Chimeric Fab	8.43E+5	2.65E-3	3.14 nM	Prepared by papain cleavage of chimeric 2.220 IgG
F4	2.00E+6	4.77E-4	0.24 nM	Humanized
L3.17	3.17E+6	3.28E-4	0.10 nM	Humanized

### 8. Humanization Results

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As discussed above, the murine anti-CD40 mAb variable region framework sequences were used to identify the most homologous human germline sequences. The H chain framework residues were 74% identical to human germline VH7 (7-4.1) and JH4 sequences while the L chain was 75% identical to the corresponding human germline VKIII (L6) and JK4 sequences. Alignment of the H and L chain variable sequences is shown in Figure 15. CDR residues, as defined by Kabat *et al.* (Kabat, E.A., et al., (1991) Sequences of proteins of immunological interest (5th Ed), Washington DC: United States Department of Health and Human Services; Kabat, E.A., et al., (1977) *J. Biol. Chem.* 252:6609-6616) are underlined and were excluded from the homology analysis. Framework residues that differed between the murine mAb and the human templates were assessed individually.

Based on structural and sequence analysis, antibody CDRs with the exception of HCDR3 display a limited number of main chain conformations termed canonical structures (Chothia, C. et al., (1987) *J. Mol. Biol.* 196:901-917; Chothia, C., et al., (1989) *Nature* 342:877-883). Moreover, certain residues critical for determining the main chain conformation of the CDR loops have been identified (Chothia (1987), *supra*; Chothia (1989), *supra*). Canonical framework residues of murine anti-CD40 were identified therefore, and it was determined that amino acids at all critical canonical positions within the H and L chain frameworks of the human templates were identical to the corresponding murine residues.

Surface-exposed murine amino acids not normally found in human antibodies are likely to contribute to the immunogenicity of the humanized mAb (Padlan, E. A. (1991) *Mol. Immunol.* 28:489-498). Therefore, framework residues differing

between murine anti-CD40 and the human templates were analyzed and based on solvent exposure were predicted to be buried or located on the surface of the antibody (Padlan (1991), *supra*). Solvent-exposed framework residues distal to the CDRs were not expected to contribute to antigen binding significantly and thus, with the exception of two H chain residues all were changed to the corresponding human amino acid to decrease potential immunogenicity. H chain residues 28 and 46 were predicted to be solvent exposed. However, H28 is located within the HCDR1 region as defined by Chothia et al., *supra*, and potentially interacts with the antigen. In addition, the lysine at H46 in the murine mAb is somewhat unusual and significantly different from the glutamic acid of the human template. Therefore, the murine and human residues at H28 and H46 were expressed in the combinatorial library (Figure 15, asterisks).

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The remaining differing framework residues, all predicted to be mostly buried within the antibody, were evaluated for: (1) proximity to CDRs; (2) potential to contact the opposite domain in the VK-VH interface; (3) relatedness of the differing amino acids; and (4) predicted importance in modulating CDR activity as defined by Studnicka et al. (Studnicka, G. M., et al. (1994) *Protein Eng.* 7:805-814). The majority of L chain framework differences in buried residues were related amino acids at positions considered not likely to be directly involved in the conformation of the CDR. However, L49 is located adjacent to LCDR2, potentially contacts the VH domain, is unrelated to the human residue, and may be involved in determining the conformation of LCDR2. For these reasons, the murine and human amino acids at L49 were both expressed in the combinatorial framework library (Figure 15, asterisk).

Analysis of the murine H chain sequence and the human template was more complex. Residue H9 is a proline in the murine mAb while the human template contains an unrelated serine residue. Position H9 may also play a role in modulating the conformation of the CDR and thus, was selected as a combinatorial library site (Figure 15, asterisks). The remaining buried framework residues that differed between murine anti-CD40 and the H chain template were at framework positions 38, 39, 48, and 91. Murine anti-CD40 mAb contained glutamine and glutamic acid at H38 and H39, respectively, while the human template contained arginine and

glutamine. Residue H38 is in proximity to the HCDR1, the glutamine—arginine change is non-conserved, and expression of glutamine at this site in murine Abs is somewhat unusual. Similarly, glutamic acid—glutamine is a non-conservative difference for buried amino acids, H39 is a potential VK contact residue, and glutamic acid is somewhat unusual in murine mAbs. Residue H48 is in close proximity to HCDR2 and H91 is predicted to be a high risk site (Studnicka (1994), *supra*; Harris, L. et al., (1995) *Prot. Sci.* 4:306-310) that potentially contacts the VK domain. Thus, both murine and human residues were expressed at H38, 39, 48, and 91 (Figure 15, asterisks).

In summary, the framework library consisted of murine CDRs grafted into the human templates. In addition, one framework residue on the L chain and seven framework residues on the H chain were deemed potentially important for maintaining the activity of the mAb. All of these sites were characterized by synthesizing a combinatorial library that expressed all possible combinations of the murine and human amino acids found at these residues. The total diversity of this library, termed Hu I, was 28 or 256 variants (Table 2 below).

Table 2: Summary of phage-expressed anti-CD40 antibody libraries.

Library	Library Positions	Size*	Screened <sup>†</sup>
Hu I	Framework	256	$2.4 \times 10^3$
Hu II	framework, HCDR3	1.1 x 10 <sup>5</sup>	2.0 x 10 <sup>6</sup>
Hu III	framework, HCDR3, LCDR3	$3.1 \times 10^{7}$	5.5 x 10 <sup>5</sup>

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The Hu I library was expressed in small-scale (<1 ml) bacterial cultures, uniform quantities of Fab released from the periplasmic space were captured in a

<sup>\*</sup>Number of unique clones based on DNA sequence. Thirty-two codons are used to encode all 20 amino acids at each CDR position.

<sup>&</sup>lt;sup>†</sup>The Hu I library was screened by ELISA using antibodies expressed in small-scale bacterial cultures (Watkins (1997), *supra*). The Hu II and Hu III libraries were plated on XL-1 Blue/agar lawns at 10<sup>5</sup> plaques per 100-mm dish and were screened by capture lift (Watkins (1998), *supra*).

microtiter plate, and the binding activity of the antibodies was compared directly by ELISA (Watkins (1997), *supra*). Although variants that bind the target antigen with affinities comparable to, or better than, the chimeric Fab were identified, the majority of Hu I clones screened were less active than the chimeric anti-CD40 Fab.

Approximately 6% of randomly selected Hu I variants displayed binding activities comparable to the chimeric Fab (data not shown). The identification of multiple Hu I variants with activity comparable to the chimeric CD40 is consistent with the interpretation that the most critical framework residues were included in the combinatorial library.

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Active clones were characterized further by titration on immobilized antigen, confirming the identification of multiple variants with enhanced affinity. For example, clone 19C11 binds the CD40 receptor with higher affinity than the chimeric Fab, as demonstrated by the shift in the titration profile (Figure 16, open circles vs. filled circles). DNA sequencing of 34 of the most active clones led to the identification of 24 unique framework combinations, each containing 2-6 murine framework residues (data not shown).

LCDR3 and HCDR3 contact antigen directly, interact with the other CDRs, and often affect the affinity and specificity of antibodies significantly (Wilson, I.A., et al., (1993) *Curr. Opin. Struct. Biol.* 3:113-118; Padlan, E.A. (1994) *Mol. Immunol.* 31:169-217). In addition, the conformation of LCDR3 and HCDR3 are determined in part by certain framework residues. To identify the most active antibody, codon-based mutagenesis (Glaser, S. M., et al., (1992) *J. Immunol.* 149:3903-3913) was used to synthesize oligonucleotides that introduce mutations at every position in HCDR3, one at a time, resulting in the expression of all 20 amino acids at each CDR residue. Each oligonucleotide encoded no more than a single amino acid alteration. The pool of oligonucleotides encoding the HCDR3 library was mixed with the overlapping oligonucleotides encoding the combinatorial framework and other CDRs to generate a framework/HCDR3 library. The diversity of this library, termed Hu II, was 1.1 x 10<sup>5</sup> (Table 2, above). A library for LCDR3 was synthesized in a similar manner. Oligonucleotides encoding the LCDR3, HCDR3, and the combinatorial framework were used to create a framework/HCDR3/LCDR3 iibrary, termed Hu III. The large

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number of framework/CDR3 combinations resulted in a library with a complexity of  $3.1 \times 10^7$  (Table 2, above).

Combining mutations in LCDR3 and/or HCDR3 with the framework library increased the potential diversity of humanized anti-CD40 variants from 256 to greater than  $10^7$ . In order to screen these larger libraries more efficiently a modified plaque lift assay, termed capture lift, was used (Watkins (1998), *supra*). Briefly, phage-infected bacteria were plated on solid agar lawns and subsequently, were overlaid with nitrocellulose filters that had been coated with a Fab-specific reagent. Following the capture of nearly uniform quantities of phage-expressed Fab the filters were probed with 5 ng/ml CD40-Ig fusion protein. Because the filters were probed with antigen at a concentration substantially below the *K*d of the Fab, only variants displaying enhanced affinity were detectable. Multiple clones displaying higher affinities were identified following the screening of  $>10^6$  variants from Hu II and  $>10^5$  variants from the Hu III library using 82-mm filters containing  $\approx 10^5$  variants per filter (Table 2).

Because of the high phage density on the filters, positive plaques were picked, replated at a lower density, and screened again. Subsequently, the variants producing the most intense colorimetric signal in the capture lift assay were further characterized by ELISA. As expected, the majority of clones identified by capture lift screening bound CD40 better than the chimeric Fab. Titration of the variants on immobilized CD40-Ig identified multiple clones displaying affinities greater than the chimeric and humanized Fab (Figure 16, compare open squares and filled triangles with circles).

The framework/CDR mutations that conferred enhanced affinity were identified by DNA sequencing. Unique variable region sequences were identified in 10/13 Hu II variants and 3/4 Hu III variants. Both the Hu II and Hu III variants contained 1-5 murine framework residues and 0-2 CDR3 mutations, as summarized in Table 3 below.

Table 3. Simultaneous optimization of framework and CDR residues identifies higher affinity variants.

Library	Clone	Murine Framework Residues*	CDR Mutations
	chimeric	(43)	0
Hu I	19C11	(2) H28, 48	0
Hu II	CW43	(3) H9, 28, 91	HCDR3, $^{101}A\rightarrow R$
	2B12	(5) H9, 28, 38, 46, 48	HCDR3, $^{101}A\rightarrow K$
Hu III	2B12	(5) H9, 28, 38, 46, 48	HCDR3, $^{101}A\rightarrow K$
	2B8	(1) H28	HCDR3, $^{101}A\rightarrow K$ ;
			LCDR3, <sup>96</sup> R→Y

<sup>\*</sup>Number of murine framework residues that differ from the most homologous human germline sequence based on definition of CDRs of Kabat et al., *supra*. The number of murine framework residues differing from the human template is indicated in parentheses. All of the framework differences between the murine mAb and the humanized versions are located on the H chain (H) at the indicated positions using the numbering system of Kabat et al.

The affinities of bacterially-expressed chimeric Fab and select variants from each of the libraries were characterized more thoroughly using surface plasmon resonance measurements to determine the association and dissociation rates of purified Fab with immobilized CD40-Ig. Chimeric anti-CD40 had a dissociation constant  $K_d = 3.14$  nM and, consistent with the screening results, many of the variants displayed higher affinities. Two of the best clones, F4 and L3.17, had  $K_d$  of 0.24 nM and 0.10 nM, respectively (Table 1). The improved affinities of the anti-CD40 variants were predominantly the result of slower dissociation rates as the association rates were very similar for all of the variants (ranging from 0.9 to 3.2 x  $10^6$  M<sup>-1</sup>s<sup>-1</sup>).

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Finally, the variants displaying enhanced affinity were tested for their ability to block the binding of gp39 ligand to the CD40 receptor. The variants all inhibited the binding of soluble CD40-Ig fusion protein to immobilized gp39 antigen in a dose-dependent manner that correlated with the affinity of the Fabs (Figure 17). For example, the most potent inhibitor of ligand binding to CD40-Ig fusion protein was variant 2B8, which was also the variant with the highest affinity for CD40 (Figure

17). Variant 2B8 displayed  $\approx$ 17-fold higher affinity for CD40 than did the chimeric Fab and inhibited ligand binding  $\approx$ 7-fold more effectively.

## Example 5

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### Mouse Model System

Applicants also developed and tested *in vivo* a rat anti-murine CD40 mAb designated 7E1-G2b and its predecessor, 7E1-G1. The generation of this antibody was performed in order to explore the potential of anti-CD40 therapy in murine models of autoimmune, inflammatory and transplant disease. The primary objective of the mouse model system was to generate an anti-murine counterpart that mimicked 2.220's complete and potent blockade of gp39/CD40 interaction while possessing weak costimulatory activity, and test it *in vivo* in standard experimental disease models.

- A. Isolation and Characterization of Anti-Murine CD40 Monoclonal Antibodies 7E1-G1 and 7E1-G2b
  - 1. Immunization, Fusion and Characterization

A recombinant murine CD40 immunoglobulin fusion protein consisting of the extracellular region of mouse CD40 fused to the hinge, CH2 and CH3 domains of a mouse IgG2a antibody (mCD40-mIg) was used to immunize an 8 week old female Lewis rat via footpad inoculation. Three days following the last immunization, leukocytes from the draining lymph nodes were fused with X63-Ag8.653 mouse myeloma cells to create rat x mouse heterohybridomas. Wells containing antibody specific for native mouse CD40 were identified for reactivity with the original mCD40-mIg immunogen by ELISA, and for reactivity with a CD40 positive mouse B cell lymphoma cell line (WEHI-231, ATCC CRL-1702). Supernatants were then tested for the ability to inhibit the binding of mCD40-mIg to soluble, recombinant mCD8-murine gp39 fusion protein, mgp39, the murine equivalent of sgp39. Approximately twelve of the most potent inhibitor master wells were cloned by a limiting dilution method.

Following cloning, functional assays were performed with culture supernatants and purified antibody in order to more accurately assess the ability of the anti-CD40

mAbs to inhibit the interaction of murine gp39 with CD40 and to determine their stimulatory properties. Inhibitory properties were measured by the ability to inhibit the binding of mgp39 to WEHI-231 using standard procedures known in the art. Stimulatory properties were measured by the induction of tight, homotypic adhesion of WEHI-231 cells and the proliferation of splenic B cells in the presence of the antibody and anti-IgM using procedures known in the art. From these results, three mAbs (5A3, 7E1-G1 and 8E1) were determined to be most like the anti-human CD40 mAb 2.220 with respect to gp39/CD40 blockade and level of costimulatory activity.

# 2. Selection of 7E1 as the Lead Anti-Murine CD40 mAb

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In vivo studies in mice were aimed at identifying which of the blocking/non-stimulatory anti-CD40 mAbs most potently suppressed specific antibody responses to a T-dependent antigen. Suppression of the IgG antibody response to SRBCs in mice with anti-murine CD40 mAb was studied. Groups of five BALB/c mice were immunized IV with 1 x 10<sup>8</sup> SRBCs and concurrently treated ip with 1 mg of anti-murine CD40 mAbs 5A3, 7E1-G1 or 8E1. As controls, groups of similarly immunized mice were treated with MR1 (hamster anti-murine gp39, positive control, 250 ug), 6E9 (rat anti-human gp39, negative control, 1 mg) or PBS. Mice were evaluated for IgG anti-SRBC titers by ELISA on days 7, 14, 21 and 35. The results indicated that when administered as a single dose of antibody at the time of antigen challenge with SRBCs, mAb 7E1-G1 was shown to be a more effective suppressor of the IgG anti-SRBC response compared to mAbs 5A3 or 8E1, and was therefore selected as the lead anti-CD40 mAb for murine studies.

## 3. Isotype Switch Variant of mAb 7E1-G1

7E1-G1 did not possess effector function characteristics comparable to that of the chimeric 2.220 anti-human CD40 mAb (i.e., rat IgG1 is not as efficient as human IgG1 at complement fixation and Fc receptor interaction) and the profile of specific antibody suppression *in vivo* for 7E1 was not as complete as that seen with the 2.220 mAb in primates. Thus, an antibody having 7E1 specificity but with a rat isotype more like human IgG1 in its effector capabilities was sought. To this end, a natural isotype switch variant of 7E1, from an IgG1 to an IgG2b, was generated by the sibselection technique (Hale et al., J. Immunol. Methods (1987) 103(1):59-67). Briefly,

an anti-CD40 mAb of the IgG2b isotype was identified by ELISA among supernatants of 96 well plates that had been seeded at 1000 cells/well with the original 7E1 hybridoma. Subsequent rounds of plating and identification of IgG2b positive wells at seeding densities of 200 and then 20 cells/well followed by two rounds of cloning by limiting dilution led to the isolation of a clonal IgG2b switch variant of 7E1, 7E1-G2b.

7E1-G2b is a legitimate switch variant of the IgG1 as demonstrated by three sets of data. First, N-terminal sequencing of the heavy chain showed that both versions were identical for the first 35 amino acid residues. Second, PCR analysis using primers specific for the variable heavy chain CDRs of 7E1-G1 yielded a band of appropriate size from cDNA obtained from either 7E1-G1 or 7E1-G2b, and not two other unrelated antibodies. Lastly, assessment of binding activity of purified lots of the two versions to immobilized mCD40-hIg in an ELISA using an anti-kappa tracer reagent yielded essentially identical titration curves.

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#### B. In Vivo Studies

1. In Vivo Comparison of 7E1-G1 to 7E1-G2b in Antibody Response Model

7E1-G1 was compared to 7E1-G2b for efficacy *in vivo* using SRBC's as the T cell dependent antigen. Groups of three to five animals were immunized iv with SRBC and concurrently treated ip with the antibody 7E1-G1 or 7E1-G2b, at 1, 0.25, or 0.1 mg of compound on day 0 as indicated in Figure 10. Anti-murine gp39 mAb MR1 served as a positive control for immunosuppressive effect. MAb 6E9 and PBS served as irrelevant mAb and no mAb controls, respectively. Mice were evaluated for anti-SRBC titers by ELISA on days 7, 14 and 21. Titer represents the calculated dilution of serum to yield an OD value =0.3 in the ELISA. As shown in Figure 10, 7E1-G2b suppressed the IgG response to SRBCs at doses where the 7E1-G1 did not.

2. 7E1-G2b Dose Response in T-dependent Antigen Mouse Model
7E1-G2b was examined in a T cell dependent primary immune response
model using SRBC as the antigen. 7E1-G2b was tested at various doses to determine
the lowest effective dose. BALB/c mice (n=5) were injected IV with 1 x 10<sup>8</sup> SRBCs

and treated with a single injection of 7E1-G2b at the indicated doses or MR1 (antimurine gp39) or PBS administered at the same time as the antigen on day 0. Shown in Figure 11 is the IgG anti-SRBC response on days 7, 16 and 28. Values reported are the ELISA absorbance value at a serum dilution of 1/50. Error bars indicate standard deviation.

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As shown in Figure 11, a single treatment with 7E1-G2b at 25  $\mu$ g/mouse (1.25 mg/kg) suppressed the IgG immune response by 87% on Day 16 and complete suppression was obtained with 50 or 100  $\mu$ g doses at Day 16. At Day 28, 50  $\mu$ g/mouse suppressed the IgG response by 89%, and 100  $\mu$ g/mouse suppressed completely. Note that MR1 was used as a positive control for immunosuppression at a suboptimal dose of 100  $\mu$ g/mouse.

3. 7E1-G2b in Preventative Collagen-Induced Arthritis (CIA) Mouse Model

A standard experimental murine model for rheumatoid arthritis, the collagen-induced arthritis model (CIA), was used to determine the effect of 7E1-G2b on prevention of arthritis. DBA/1J male mice (6-8 weeks) were injected with 200 ug of chicken collagen type II (CII) in complete Freund's adjuvant intradermally on day 0. Treatment with 7E1-G2b at 250 µg/dose was administered IP every 4 days starting on day 7. The control group was treated with PBS on the same dosing schedule. All mice were boosted with CII in incomplete Freund's adjuvant on day 21. Mice were observed daily for paw swelling and subjectively scored on a scale of 0-3 with 3 equal to maximum swelling and erythema. Paws were also measured with calipers daily. The clinical score reported was derived by summation of the score of each paw at the time of sacrifice and dividing by the total number of animal in each group. The values reported are the median range of the groups.

Arthritis development, and hence joint inflammation in the mice, was completely inhibited by therapy with 7E1-G2b as shown in Table 4 below. Mice treated with 7E1-G2b were completely free of disease through 90 days.

Table 4. Treatment of Collagen-Induced Arthritis

Tx Group	Arthritis Incidence	Median (Range)  Day of onset	Median (Range) Clinical score	Median (Range) Paw measure
7E1-G1	0/5	0	0	0.075

7E1-G2b	0/5	0	0	0.075
PBS control	4/4	30 (27 - 32)	3.5 (3 - 4)	0.114 (0.110-0.117)

As demonstrated above, the antibodies of the present invention are potent immunomodulators, with therapeutic uses against a variety of disease.

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The present invention encompasses chimeric and humanized antibodies as described above with additional conservative amino acid substitutions which have substantially no effect on CD40 binding. Conservative substitutions typically include the substitution of one amino acid for another with similar characteristics, e.g., substitutions within the following groups: valine, glycine; glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine.

In one aspect, the present invention is directed to producing the chimeric and/or humanized antibodies as described above by expressing recombinant DNA segments encoding the murine light variable chain and heavy variable chain (or portions thereof), attached to DNA segments encoding the human constant regions. Exemplary DNA sequences designed in accordance with the present invention code for the polypeptide chains comprising all or a portion of the light chain variable region as shown in SEQ ID NO:1 or its deposited ATCC clone, and/or all or a portion of the heavy chain variable region as shown in SEQ ID NO:2 or its deposited ATCC clone.

Also encompassed within the present invention are the disclosed heavy and light chain variable regions and active or functional parts thereof. The immunologically competent or functional form of the protein or part thereof is also referred to herein as a "light/heavy chain variable region or biologically active portion thereof". In the present case, a biologically active portion thereof comprises a portion of said light or heavy chain which, when incorporated into an antibody, still permits the antibody to bind to human CD40.

Specifically encompassed within the present invention are nucleic acid sequences encoding the variable heavy chain and the variable light chain of an antibody of the present invention. For example, nucleotides 1057 through 1422 (SEQ ID NO:5) of Figure 13 provide a preferred nucleic acid sequence encoding a variable

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heavy chain of an antibody of the present invention; nucleotides 1065 through 1388 (SEQ ID NO:6) of Figure 14 provide a preferred nucleic acid sequence encoding a variable light chain of an antibody of the present invention. SEQ ID NO:7 and SEQ ID NO:11 show preferred nucleic acid sequences encoding variable light chains of humanized antibodies of the present invention; SEQ ID NO:9 shows a preferred nucleic acid sequence encoding a variable heavy chain of a humanized antibody of the present invention. Plasmids comprising the polynucleotides shown in SEQ ID NO:7, SEQ ID NO:9 and SEQ ID NO:11 have been deposited with the ATCC.

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Chimeric and/or humanized antibodies that bind to human CD40 and that comprise polypeptides that are substantially homologous to, or that show substantial sequence identity to, the variable light and heavy chain sequences disclosed herein are also contemplated by the present invention. For example, chimeric antibodies comprising a light chain region that exhibits at least about 85% sequence identity, more preferably at least about 90% sequence identity, even more preferably at least about 95% sequence identity, and most preferably at least about 98% sequence identity with the light chain region as shown in SEQ ID NO:4 are included within the scope of the present invention. More particularly, chimeric antibodies comprising a variable light chain region that exhibits at least about 85% sequence identity, more preferably at least about 90% sequence identity, even more preferably at least about 95% sequence identity, and most preferably at least about 98% sequence identity with the variable light chain region as shown in SEQ ID NO:1 are also included within the scope of the present invention. Also within the scope of the present invention are humanized antibodies comprising a light chain region that exhibits at least about 85% sequence identity, more preferably at least about 90% sequence identity, even more preferably at least about 95% sequence identity, and most preferably at least about 98% sequence identity with the light chain region as shown in SEQ ID NO:8 and/or SEQ ID NO:12.

Additionally, chimeric antibodies comprising a heavy chain region that exhibits at least about 85% sequence identity, more preferably at least about 90% sequence identity, even more preferably at least about 95% sequence identity, and most preferably at least about 98% sequence identity with the heavy chain region as

shown in SEQ ID NO:3 are included within the scope of the present invention. More particularly, chimeric antibodies comprising a variable heavy chain region that exhibits at least about 85% sequence identity, more preferably at least about 90% sequence identity, even more preferably at least about 95% sequence identity, and most preferably at least about 98% sequence identity with the variable heavy chain region as shown in SEQ ID NO:2 are also included within the scope of the present invention. Additionally, humanized antibodies comprising a variable heavy chain region that exhibits at least about 85% sequence identity, more preferably at least about 90% sequence identity, even more preferably at least about 95% sequence identity, and most preferably at least about 98% sequence identity with the variable heavy chain region as shown in SEQ ID NO:10 are also included within the scope of the present invention.

The DNA segments typically further comprise an expression control DNA sequence operably linked to the chimeric or humanized antibody coding sequences, including naturally-associated or heterologous promoter regions. Preferably, the expression control sequences will be eukaryotic promoter systems in vectors capable of transforming or transfecting eukaryotic host cells, but control sequences for prokaryotic hosts may also be used. Once the vector has been incorporated into an appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences and, as desired, the collection and purification of the variable light chain, heavy chain, light/heavy chain dimers or intact antibody, binding fragments or other immunoglobulin form may follow. (See, Beychok, S., "Cells of Immunoglobulin Synthesis", Academic Press, N.Y. (1979)). Single chain antibodies may also be produced by joining nucleic acid sequences encoding the VL and VH regions disclosed herein with DNA encoding a polypeptide linker.

Prokaryotic hosts, such as E. coli, and other microbes, such as yeast, may be used to express an antibody of the present invention. In addition to microorganisms, mammalian tissue cell culture may also be used to express and produce the antibodies of the present invention. Eukaryotic cells may be preferred, because a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed in the art, and include the CHO cell lines, various COS cell lines, HeLa

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cells, myeloma cell lines, and hybridomas. Expression vectors for these cells can include expression control sequences, such as a promoter or enhancer, and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences, all known in the art.

The vectors containing the DNA segments of interest (e.g., the heavy and/or light chain encoding sequences and expression control sequences) can be transferred into the host cell by well-known methods, which vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts. (See, e.g., Maniatis, et al., "Molecular Cloning: A Laboratory Manual", Cold Spring Harbor Press (1982)).

Once expressed, the whole antibodies, their dimers, individual light and heavy chains, or other immunoglobulin forms of the present invention, can be purified according to standard procedures in the art, including ammonium sulfate precipitation, affinity columns, column chromatography, gel electrophoresis and the like. Substantially pure immunoglobulins of at least 90 to 95% homogeneity are preferred, and 98 to 99% or more homogeneity are most preferred, for pharmaceutical uses.

The antibodies of the present invention will typically find use in treating antibody mediated and/or T cell mediated disorders. Typical disease states suitable for treatment include graft versus host disease and transplant rejection, and autoimmune diseases such as Type I diabetes, psoriasis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and myesthenia gravis.

The antibodies and pharmaceutical compositions of the present invention are particularly useful for parenteral administration, i.e., subcutaneously, intramuscularly or intravenously. The pharmaceutical compositions for parenteral administration will commonly comprise a solution of the antibody dissolved in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers can be used, all well known in the art, e.g., water, buffered water, saline, glycine and the like. These solutions are sterile and generally free of particulate matter. These pharmaceutical compositions may be sterilized by conventional well known sterilization techniques. The compositions may contain pharmaceutically acceptable auxiliary substances as

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required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents and the like, for example, sodium acetate, sodium chloride, potassium chloride, calcium chloride, sodium lactate, human albumin, etc.

The compositions containing antibodies of the present invention can be administered for prophylactic and/or therapeutic treatments. In therapeutic application, compositions are administered to a patient already suffering from a disease, in an amount sufficient to cure or at least partially arrest the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose". Amounts effective for this use will depend upon the severity of the disease state and the general state of the patient's own immune system, and can be determined by one skilled in the art.

In prophylactic applications, compositions containing antibodies of the present invention are administered to a patient not already in the disease state to enhance the patient's resistance (suppress an immune response). Such an amount is defined to be a "prophylactically effective dose". In this use, the precise amounts again depend upon the patient's state of health and general level of immunity. A preferred prophylactic use is for the prevention of transplant rejection, e.g., kidney transplant rejection.

Although the present invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

## We Claim:

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1. A light chain variable region comprising all or a biologically active portion of an amino acid sequence as shown in SEQ ID NO:1 (Figure 4a).

- 2. A heavy chain variable region comprising all or a biologically active portion of an amino acid sequence as shown in SEQ ID NO:2 (Figure 4b).
  - 3. A chimeric antibody which binds to human CD40 comprising a light chain and a heavy chain, said light chain comprising the light chain variable region of claim1.
- 4. A chimeric antibody which binds to human CD40 comprising a light chain and a heavy chain, said heavy chain comprising the heavy chain variable region of claim 2.
  - 5. The chimeric antibody of claim 3 wherein said heavy chain comprises the heavy chain variable region of claim 2.
- 6. A chimeric antibody which binds to human CD40, comprising a light chain and a heavy chain, said light chain comprising all or a biologically active portion of an amino acid sequence as shown in SEQ ID NO:4 and said heavy chain comprising all or a biologically active portion of an amino acid sequence as shown in SEQ ID NO:3.
- 7. A nucleic acid molecule comprising a nucleotide sequence encoding the light chain variable region of claim 1.
  - 8. A nucleic acid molecule comprising a nucleotide sequence encoding the heavy chain variable region of claim 2.
  - 9. An expression vector comprising a nucleic acid sequence of claim 7.
  - 10. An expression vector comprising a nucleic acid sequence of claim 8.
- A humanized antibody comprising a portion of the light chain variable region of claim 1.
  - 12. A humanized antibody comprising a portion of the heavy chain variable region of claim 2.
  - 13. A pharmaceutical composition comprising the chimeric antibody of claim 5.
- 30 14. A pharmaceutical composition comprising the chimeric antibody of claim 6.

15. A chimeric antibody which binds to human CD40 comprising a light chain variable region and a heavy chain variable region, wherein said light chain variable region comprises an amino acid sequence having at least 90% sequence identity to the light chain variable region of claim 1.

- A chimeric antibody which binds to human CD40 comprising a light chain variable region and a heavy chain variable region, wherein said heavy chain variable region comprises an amino acid sequence having at least 90% sequence identity to the heavy chain variable region of claim 2.
- 17. A method of treating a patient suffering from a T cell mediated disorder, said method comprising administering to said patient a therapeutically effective dose of a pharmaceutical composition of claim 14.
  - 18. The nucleic acid molecule of claim 7 comprising the nucleotide sequence as shown in SEQ ID NO:6.
  - 19. The nucleic acid molecule of claim 8 comprising the nucleotide sequence as shown in SEQ ID NO:5.

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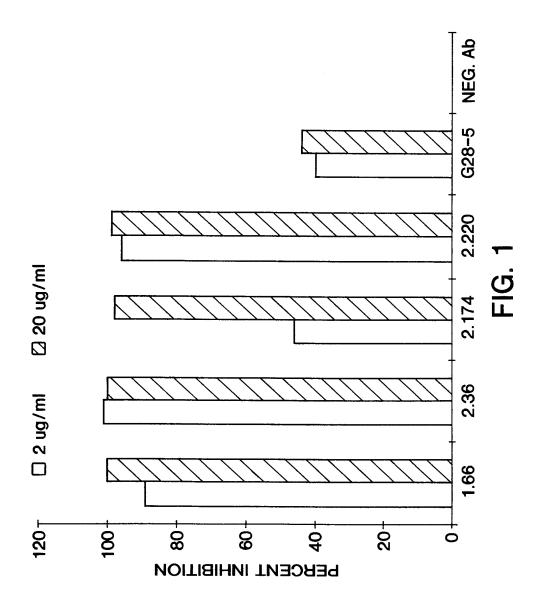
- 20. The chimeric antibody of claim 6 comprising a light chain amino acid sequence as shown in SEQ ID NO:4 and a heavy chain amino acid sequence as shown in SEQ ID NO:3.
- The humanized antibody of claim 11 comprising a light chain variable region as shown in SEQ ID NO:8.
  - 22. The humanized antibody of claim 11 comprising a heavy chain variable region as shown in SEQ ID NO:10.
  - 23. The humanized antibody of claim 12 comprising a light chain variable region as shown in SEQ ID NO:8.
- 25 24. The humanized antibody of claim 12 comprising a heavy chain variable region as shown in SEQ ID NO:10.
  - 25. The humanized antibody of claim 11 comprising a light chain variable region as shown in SEQ ID NO:8 and a heavy chain variable region as shown in SEQ ID NO:10.
- The humanized antibody of claim 11 comprising a light chain variable region as shown in SEQ ID NO:12.

27. The humanized antibody of claim 26 comprising a heavy chain variable region as shown in SEQ ID NO:10.

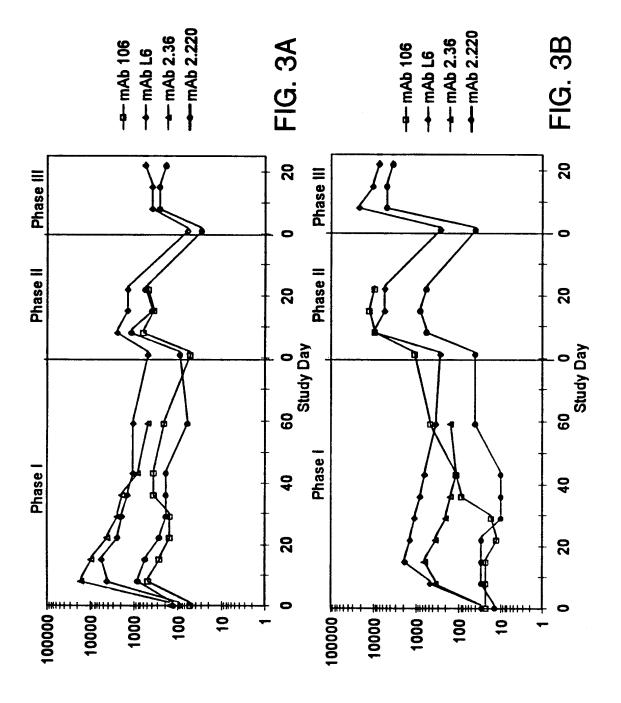
28. The humanized antibody of claim 11 comprising a light chain variable region as shown in SEQ ID NO:12 and a heavy chain variable region as shown in SEQ ID NO:10.

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- 29. A pharmaceutical composition comprising a humanized antibody of claim 25.
- 30. A pharmaceutical composition comprising a humanized antibody of claim 28.



PHASE		<u></u>	풉	PHASE II			<b>-</b>	PHASE III	=
mAb 2.220									
M mab INJECTED 0 8 15 22 29 36 43	29 BLEED		ω	15	22	<b>—</b>	<b>∞</b>	15	22
SRBC 1°		SRBC 2° VKLH 1°	IC 2°				SRBC 3° V KLH 2°		
		•	F	FIG. 2					



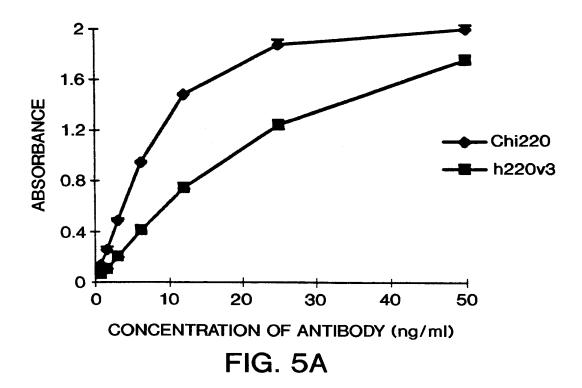
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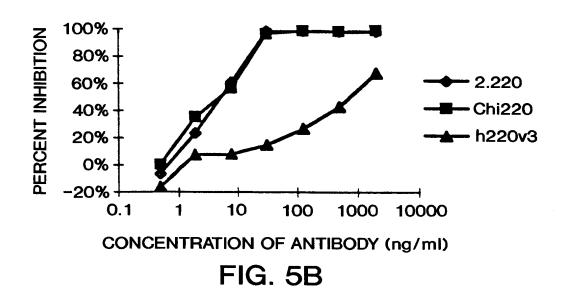
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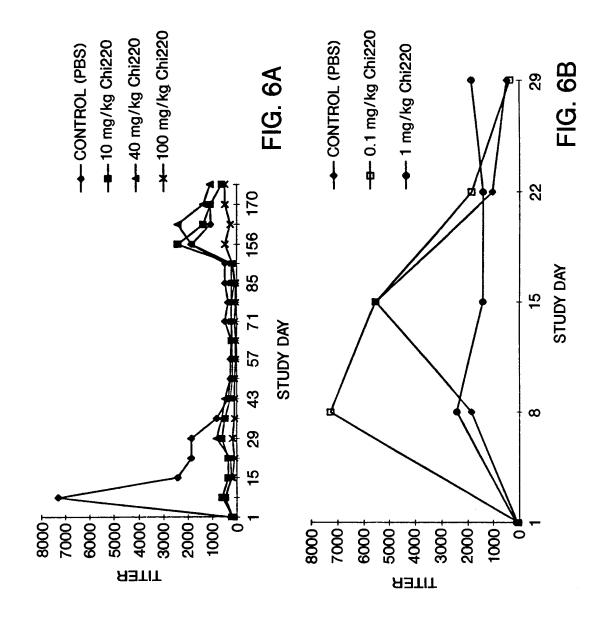
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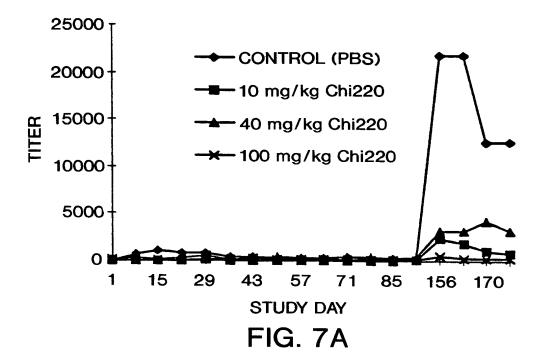
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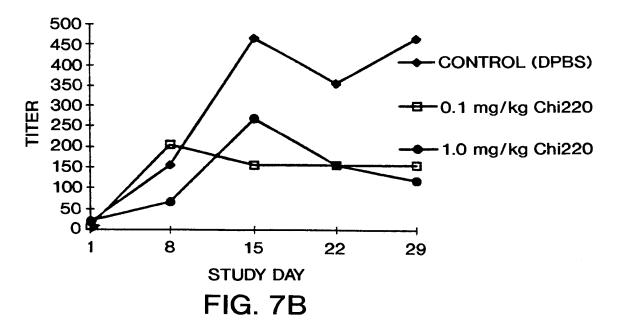
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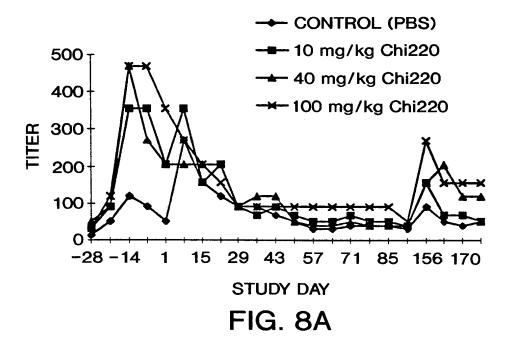


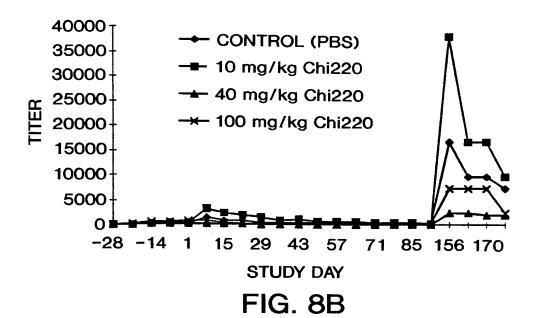


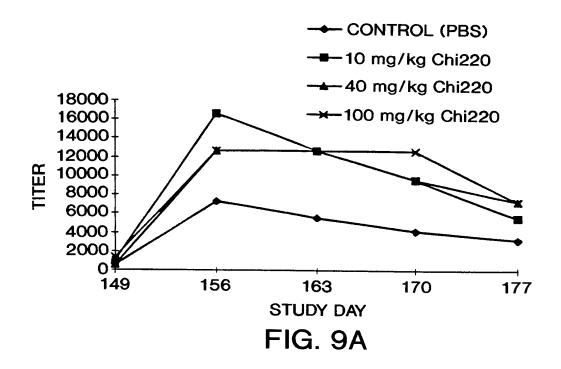


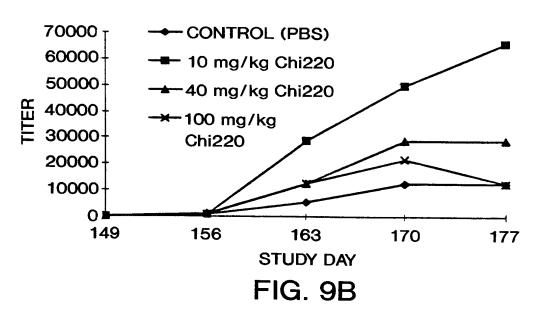


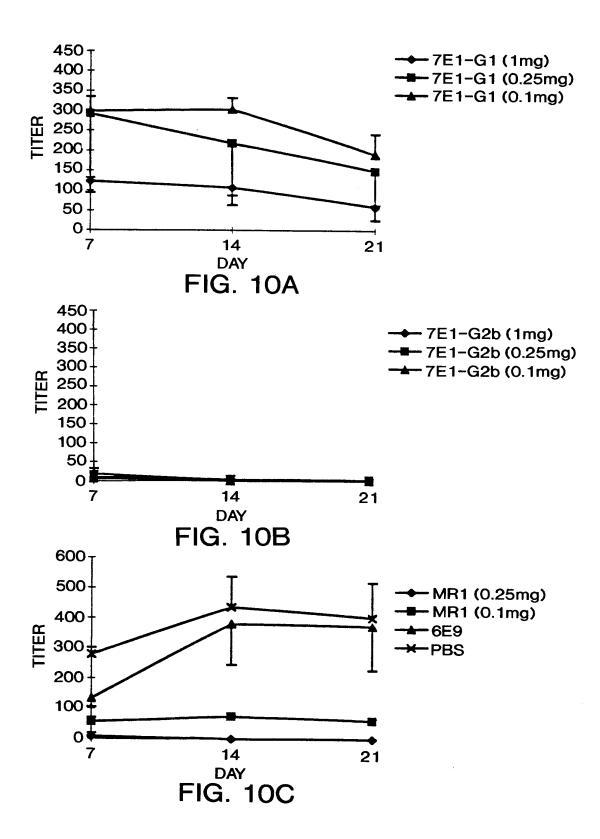


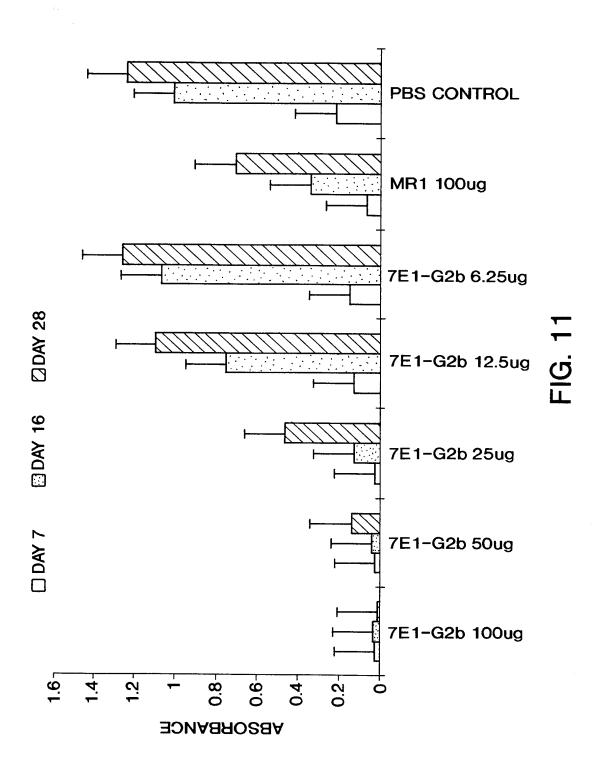




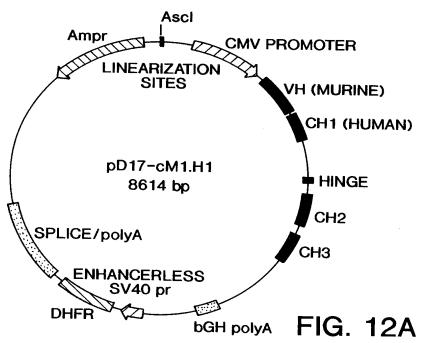




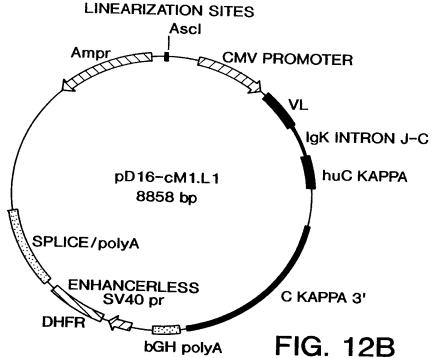








LIGHT CHAIN chi220



GAGGATCGG GAGATCTGCT AGGTGACCTG AGGCGGCGG GCTTCGAATA GCCAGAGTAA ACCCCTATG GTCGACTCT AGTACAATCT GCTCTCATGG ATTCCCCTATG GTCGACTCT AGTACAATCT GCTCTCATGG TCGCTGTCTTTTT TAATTTTATTTATTTATT TTAGACTGCG CAGTCTCCCG ATTCCCCTATG GTCGACTCT AGTACAATCT GCTCTCATGGC AGCAAAATT TAAGCTACAA ACACTCGCTGCT GAGTGCGCT AGTACATCGC CTGCCACACTCT AGGCAAAATT TAAGCTACAA ACACTCGCTG TATCAGGGCC AGATATACGC GTTGACATTC TAGGCTATGG CTTTTAGGCT AGTATATAAT TACGGGGCCC AGATATACGC GTTGACATTC ATTATTACTCAC GTTGACTGACG ACTACATATA TACGGGGCCC TGCTGACCGC CCACACACC CCGCCCATTG ACCTCAATAA ACTACACTATT TCCCATAGTA ACCCCAATTAG GCCCATATATC GCGCCATTATTCCA TTGACGTCAA AGCACACCACC ATTATGACGT ACACTCACCAC TTGGCAGTAC ATCACCTCAA ATCACCCCC TTATTAGCGT AAATGCCCCC CTGGCAGCCC CTGGCACTC TTGACGTCAA AGTACCCCC ATTATTAGCGT AAATGCCCCC CTGGCAGTAC TTGACGTCAA ATCACCCCC ATTATTAGCGT AAATGCCCCC CTTGGCAGTAC ACCCCACTTA TCCCCACTAC ACTACCCCC ATTATTAGCGT AAATGCCCCC CTTGGCAGTAC ACCCCACTTA TCCCCACTAC ATGACCCCCA ATGACCCCAT TGACGTCAAT AGGCCGTGAAT ACCGCGTATA TCCCCACTACA ATGACCCTAT ATTATTATAGA CAACTCCCCC CCATTGACCAC AAATGCACCC AAATCCAACGG AAATCAACCG ATTCCTATTTGGCA GAACCCCAC CTTGACCATTAC CAACTCCAGGGGAT ACACTCCCACT TGACGTCAAT AGGCGTGAAATGCC AAATCCAACGG GACTTCCCAA ATATACCAC CACCCACTGGAGAGCC CATTGACCAC AAATCCAACGG GACTTCCCAA ATATACCAC CACCCACTGGAGAGCC CACTCCCACAC CTGCACACTCCAC ATATATACCAC CACCCACTGGAGAGCC CACTCCCACGA TCCACTCAGGGCT ATATACCAC CACCCACTGGAGAGCC CACTCCCACGA TCCACTCAGGCCT ATATACCAC CACCCACTGGAGAGCC CACCCCCATTGACC TGACGTTGGC CTTACCAAAAT CTCTTCTTGG TGGCAGCAC AAAGGCCCC CACCCCCATTGACC CACCCCCATTGACC CTGACGCTCC AAATCCACCCC ATATACACACCCAC CTCCCCACAC CTCCCCACA TCCACCCCAC TCCACCCCAC AAAGCCCAT TCCACACTCCAC CACCCCCACTCCCCCCCCCC	_						
1211 ATCCCCTATG GTGGACTCT AGTACATCT GCTCTATGC CGACAAATT TAAGCTACA 241 CAAGGCAAG CTTGACCGAC AATTGCATGA AGAATCTGCT TAGGGTTAGG CGTTTTGCGC 241 TAGGTACAA TAGCACGAC AATTGCATGA AGAATCTGCT TAGGGTTAGG CGTTTTGCGC 241 TAGGTAAA TAGCAGGGCC AGATATACCG GTTGACATTGA ATTATTCACT AGTTATTAAT 241 TAGGTAAA TAGCAGGGCC AGATATACCG CTTGACATTGA GTTATTTAACT 241 TAGGTAAA TGGCCGGCCCT GGCTGACCGC CCACCACCACC CCGCCCATTG ACGTCAATAA 241 TAGGTAAA TGGCCGGCCT GGCTGACCGC CCACCACCACC CCGCCCATTG ACGTCAATAA 242 TATTACGGTA AACTGCCCAC TAGGACCGC CCACCACACC CCGCCCATTG ACGTCAATAA 243 TAGCAGTATGT TCCCATAGTA ACGCCACATGA GGACTTTCCA TTGACGTCAC TAGCACTACA 244 TATTACGGTA AACTGCCCAC TAGGACCGC CTGGCATTA TGCCCAGATCA TGGCTGCATTA 245 TAGCTTTCC TACTTGGCAG TACATCTACC TATTACCACCCCAC TAGTTGCACTTAC AGTGCACTTA 246 GGACTTTCC TACTTGGCAG TACATCTACC TATTACCACCCAC TATTACCACCCAC TACATCTACC AATACACCAC TACATCTACC AATACACCAC TACATCTACC AATACACCAC TACATCTACCACCACAC TCCACCACACAC TCCACCACCAC TCGACCACACAC TCCACCACACAC TCCACCACACAC TCGACCACACAC TCCACCACCAC TCGACCACACAC TCCACCACCAC TCGACCACACC TCGACCACACC TCGACCACACC TCGACCACACC TCGACCACACC TCGACCACACC TCGACCACCAC TCCACCACCAC TCGACCACACC TCGACCACCAC TCCACCACCACC TCGACCACCAC TCCACCACCACC TCCACCACCAC TCCACCACCACC TCCACCACCAC TCCACCACCAC TCCACCACCAC TCCACCACCACC TCCACCACCAC TCCACCACCAC TCCACCACCAC TCCACCAC	1	GACGGATCGG	GAGATCTGCT	AGGTGACCTG	AGGCGCGCCG	GCTTCGAATA	GCCAGAGTAA
TRACTECCTGC TTGTGTGTTG GAGGTGCTG AGTAGTGGCG GAGAAAATT TAGGTACAA AGGGCAAGG CTTGACCGGC AGATATACGC GTTGACAATTG ATTATGACT AGTATCAAT TACGGGGTCA TATATGACTG AGATATACGC GTTGACAATTG AGTATCAAT TACGGGGTCA TAGATCAATTG GAGATTACGC GTTACAATTAC ATTACGGTAAA TACGGGCTCA TGGCACAATTA GAGATCACCC GTTACAATTAC TTACGGTAAA TGGCCCACCT TGGCAGACGC CCAACGACCC CCGCCCATTG ACTCAATAA ATTACGGTAAA AGCCCCAATGA GGACTTTCCA TTGACGTCAA AGTACGCCCC TATTGACGT AACTGCCCA TTGGCAGTAC ATCAAGTTA TCATATGCCA AGTACGCCCC CTATTGACGT AACTGCCCA TAGACGCA TACAAGTTA TCATATGCCA AGTACGCCCC CTATTGACGT AACTGCCAC TACTTGAC TATTAGCCA AGTACGCCCC CTATTGACGT AACTGCCAC TACTTGAC TATTAGCCA AGTACGCCCC TCTATTGACGT CAATCAAG TACAACTTACC TATTAGCCATA TCACAGTTAC ATGACCTTAT CCCCCCCAT TGACGTCACAT GGGCGTGGAT AGCGGTTTGC TCACGGGGA TTTCCAAGTC CTATTGACA CAACTCCACC CCATTGACGC AAATGGGGGG TAGCGCTTACC AGTTCCAAGTC CTATTAGAAG CAACTCCACC CCATTGACGC AAATGGGGGG TAGCGGTGACA AATTACACGG GACTTTCCAA AATGCCTAA CAACTCCACC CCATTGACCG AAATGGGGGG TAGCGCTTACG CTTATACCG CACTTACAG CACTTCCAAGTC CTTATATAGA CAACTCCACC CCATTGACCG AAATGGGGGG TAGCGCTACC CCTTTCCTAG TTATATACGAC TCACTATAG GAGACCCAA GCTTGGTACCA TGCCTACTGG CTTATCGGAAGTC CTCTTCTTGG TGGCAGACCAC ACCGTACCAAG CTTGGTACCA TGCCTACCAG CTTTGACGAAGCC CTCTTCTTCTG TGGCAGCACC ACCGTACCAAG CTTGGTACCA TGCCATTGGT CCAACTCGGAAGC CTCTTCTTCTG TGGCAGCACC ACCGTGCCA AGAAGTCCCAC TGCTAACCAG GACTTCCCCCAACCC TGCTTACACCA TGCCAACCCAA TGCCTACACCAACCAACCAACCACCACC CTCCAACCACAA AAATGACTCAA GAGACCCACC TGCCAACCACCAACCACCACC CTCCAACCACACCAC	61	CCTTTTTTTT	TAATTTTATT	TTATTTTATT	TTTGAGATGG	AGTTTGGCGC	CGATCTCCCG
241 CAAGGCAAGG CTTGACCGAC AATTGCATGA AGAATCTGCT TAGGGTTAGC GCTTTTGCGG CGTTCAGGA TGTACGGGGC CAATATACGG GTGACACTA AGTATTCATT 361 AGTAATCAAT TACGGGGTCA TTAGTTCATA GCCCATATAT GAGGTTCGC GTTACATAA 481 TACGGTAAA TGGCCCGCCT GGCTGACGC CCAACGACCC CCGCCCATTG AGTACATAA 481 TACGGTAAA TGGCCCGCCT TGGCACGC CCAACGACCC CCGCCCATTG AGTACATAA 481 TACGGTAAA TGGCCCGCT TTGGCAGTAC ATCAAGTTA TCACCACTCAATAA 481 TACGGTAAA ACTGCCCAC TTGGCAGTAC ATCAAGTTA TCACCAGTCA AGTACGCCCC 4ATTTAGCGT AACTGCCCAC TTGGCAGTAC ATCAAGTTA TCCCCAGTAC AGTACGCCCC 4ATTTAGCGT AACTGCCAC TACATCACG TACTTAGCCA AGTACGCCCC 4GGCATTTCC TACTTGCGA TACATCACG TATTAGTCAT TGCCCAGTAC ATGGGCATTA 4TTTAGACGT AACTGCCAC TACATCACG TACATCACG TACTTACCA AGTACGCCCC 4GTTTTGCGA GTACATCACT GGGCGTGGAT AGCGGGTTTA TCCCCAAGTC 4ATTAGACGT TACATCACT GGGCGTGGAT AGCGGGTTTA TCCCCAAGTC 4ATTAGACG GTACATCAAT GGGCGTGGAT AGCGGGTTGA CTCCAAGTC 4ATTAGACGA TACACTCAC GGGACTTTT TTTGGCACCA AAATCACGG GACTTCCAAG 4ATTAGACGA TCACATTAGAG GAGACCCAC TTCCTAAGTC AAATCACGG TACATCAGAA 4ATCACACC 4ATTAGACGA TCACATTAGAG AGAACCCAC TTCCTTATACC AAATCACGG TAGACTAGAA 4ATCACACCAC TCACTTACAGC AAATCACCAC TGCTTACTGG TATTCGAAA 4ATCACACCAC TCACTTACAGC AAATCACCAC TTGCTTACTG TACATCAGAA 4ATCACACCAC TCACTTACAGC AAATCACCAC TGCTTACTGG TATTCGAAA 4ATCACACCAC TCACTTACAGC AAATCACCAC TCACTCCCAAGC TTGACTACAC TGGAAGCTTC TGGAAGCTTC 4ATTACACACCAC TCACTCAACCAC CACCTCCCAGACCT TACACTCACACC TACACCACC TACACCACCAC TACACCACCACCACCACCACCACCACCACCACCACCACCA		ATCCCCTATG	GTCGACTCTC	AGTACAATCT	GCTCTGATGC	CGCATAGTTA	AGCCAGTATC
TGCTTCGCGA TGTACGGGC AGATATACGC GTTGACATTG ATTATGACT AGTTATTAAT TACGGGTAAA TACGGGGTCA TTAGTTCAATA GCCCATATAAT GGAGTCCCC GTTACATAAC TTACGGTAAA TGGCCGCCT GGCTGACCGC CCAACGACC CCGCCCATTG ACGTCAATAAC TTACGGTAAA TGGCCGCCT TGGCTGACCGC CCAACGACCA CCGCCCATTG ACGTCAATAAC TTACGGTAAA TGCCCCAC TTGGCAGTAC ATCAAGTCTA TCACTAGCCA AGTACGCCCC CTATTGACGT AACTGCCCAC TTGGCAGTAC ATCAAGTCTA TCACTAGCCA AGTACGCCCC CTATTGACGT AACTGCCGC TACTTGGCAGTA ATCAAGTCTA TCACTAGCCA AGTACGCCCC CTATTGACGT AACTGCAG TACATCTACG TATTAGTCTA TCACTAGCCA AGTACGCCCC TACTTGGCAG GTACACTCAG GGACTTTCA TTTGGCAGTA CATGACCTTAT GGTTTTGGCA GTACACCAAT GGGGGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC CTACTCGCCCAT TGACCCTCAAT GGGGGTTGAT TTTGGCACCAC AAATCACCGG TCTATTAAACGAC TGACCTCAAT GGGGGTTGTA TTTGGCACACA AAATCACCGG TTTATATATACGAC CAACCCCC CCATTGACGC AAATCACCG GACTTTCCAA TATAATCGCAC TCGCTACACT GGACCCCAC TGCTTACTGG GACTTTCCAA TATAATCGCA CTCACTATAG GAGACCCCAC CTTGGTACCA TGGCATTGGAC CTGGAGAATC CTCTGAGTTGA AGAACCCCC TGGCTACAC TGGCTCACAC TGCATTGGAC TTAACAGAC ACCACTATAGG GAGACCACT AGAACTCACA TGGACTTGAC CTGGAGATC CTCTGAGCTGA AGAAGCCTC TGGAGACCAC ACTCCCCAGA TCCAGTTGGA CTGAGATTGCC LTATTGACAACTA CTGGAATCCC ACTGCCCAGA TCCAGTTGGA CCAATTTGGA TTACACAACTA CTGGAATCCC TGGAGACCACT TGGATTCCAA TGGACTTGAC CTGAGATTGCC LTATTGACAACTA CTGGAATCCC TGGAGTGCCA AAATATTGAA CAGCCCACT TGGATGCCC AAATCATCAG GAAACGGTT TGGGTGAACTACACT LTATTGCTTACT TGGAAACCCC TGCACCAC AAATCATCAG GAAACGGTT CAACCTACACT LTATTGCTTACT TGGAAACCCC TCCCCAAC AAATCATCAG AGACCTCCAC CAAGGCCCAC LAGCCCCACCC TGGACACCC TCCCCCAAC CCCCACCCC CACCCCCAAC CCCCACCCC CACCCCCACC CCCCCC	181	TGCTCCCTGC	TTGTGTGTTG	GAGGTCGCTG	AGTAGTGCGC	GAGCAAAATT	TAAGCTACAA
TGCTTCGCGA TGTACGGGC AGATATACGC GTTGACATTG ATTATGACT AGTTATTAAT TACGGGTAAA TACGGGGTCA TTAGTTCAATA GCCCATATAAT GGAGTCCCC GTTACATAAC TTACGGTAAA TGGCCGCCT GGCTGACCGC CCAACGACC CCGCCCATTG ACGTCAATAAC TTACGGTAAA TGGCCGCCT TGGCTGACCGC CCAACGACCA CCGCCCATTG ACGTCAATAAC TTACGGTAAA TGCCCCAC TTGGCAGTAC ATCAAGTCTA TCACTAGCCA AGTACGCCCC CTATTGACGT AACTGCCCAC TTGGCAGTAC ATCAAGTCTA TCACTAGCCA AGTACGCCCC CTATTGACGT AACTGCCGC TACTTGGCAGTA ATCAAGTCTA TCACTAGCCA AGTACGCCCC CTATTGACGT AACTGCAG TACATCTACG TATTAGTCTA TCACTAGCCA AGTACGCCCC TACTTGGCAG GTACACTCAG GGACTTTCA TTTGGCAGTA CATGACCTTAT GGTTTTGGCA GTACACCAAT GGGGGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC CTACTCGCCCAT TGACCCTCAAT GGGGGTTGAT TTTGGCACCAC AAATCACCGG TCTATTAAACGAC TGACCTCAAT GGGGGTTGTA TTTGGCACACA AAATCACCGG TTTATATATACGAC CAACCCCC CCATTGACGC AAATCACCG GACTTTCCAA TATAATCGCAC TCGCTACACT GGACCCCAC TGCTTACTGG GACTTTCCAA TATAATCGCA CTCACTATAG GAGACCCCAC CTTGGTACCA TGGCATTGGAC CTGGAGAATC CTCTGAGTTGA AGAACCCCC TGGCTACAC TGGCTCACAC TGCATTGGAC TTAACAGAC ACCACTATAGG GAGACCACT AGAACTCACA TGGACTTGAC CTGGAGATC CTCTGAGCTGA AGAAGCCTC TGGAGACCAC ACTCCCCAGA TCCAGTTGGA CTGAGATTGCC LTATTGACAACTA CTGGAATCCC ACTGCCCAGA TCCAGTTGGA CCAATTTGGA TTACACAACTA CTGGAATCCC TGGAGACCACT TGGATTCCAA TGGACTTGAC CTGAGATTGCC LTATTGACAACTA CTGGAATCCC TGGAGTGCCA AAATATTGAA CAGCCCACT TGGATGCCC AAATCATCAG GAAACGGTT TGGGTGAACTACACT LTATTGCTTACT TGGAAACCCC TGCACCAC AAATCATCAG GAAACGGTT CAACCTACACT LTATTGCTTACT TGGAAACCCC TCCCCAAC AAATCATCAG AGACCTCCAC CAAGGCCCAC LAGCCCCACCC TGGACACCC TCCCCCAAC CCCCACCCC CACCCCCAAC CCCCACCCC CACCCCCACC CCCCCC	241	CAAGGCAAGG	CTTGACCGAC	AATTGCATGA	AGAATCTGCT	TAGGGTTAGG	CGTTTTGCGC
AGTANTCART TACGGGGGTC TATACTARA GCCCATARAT GAGTTCCGC GTACATARA 121 TACGGTANA TGGCCGGCCT GGCTCACCGC CCACGACGCC CGGCCCATTG ACGTCAATAA 122 TATACGGTAN ACTCCCAC TTGCCATACTA ACGCCATAGA GGACTTTCCA TTGACGTAN TGGGTGGACT 123 TATTACAGGTA AACTGCCCAC TTGGCAGTAC ATCAATGTA TCATATGCCA AGTACGCCCC 124 TATTACAGGTA AACTGCCCAC TACGCGATAC ATCAATGTAT TCATATGCCA AGTACGCCCC 125 TATTAGAGTA TACACTAGG ATCAATGACGCCCCCTTGGCATTA TGCCCAGTAC ATGACCTTAT 124 GGGACTTTCC TACTTGGCAG TACACTAGC ATCAATGACG CCTCTGGCATTA TGCCCAGGTA ATGGGGATGCCCC 125 TACACTAAC GGGCTTGAT TGCCCAAGTC ATGGGGATG 125 TCCACCCCAT TGACGCAAT GGGCATTGT TTTTGGCACCA AAATCAACGG GACTTTCCAA 126 TCCACCCCAT TGACGCCAAT GGGAATCACAC TGCCTAAGCG ACTTTCCAAGC 127 TATATACAGCA CACCTCCCC CCATTACACC AAATCAACCG GACTTCCAAGTC 128 TCTATATAAA CAACTCCCC CCATTACACC AAATCACCAC TGCTTACTGG 128 TCTATATAACACA CTCACTATAGG GAGACCCAAC CTTGGTACCA TGCACTGGAC 128 TCTATATACACAC TCACCTATAGG GAGACCCAAC CTTGGTACCA TGCACTGGAC 128 TCTATATACACAC TCACCTATAGG AGAACCCAC TGCTACCA TGCATGGAC 128 TCTACATATAG GAGACCCTC TGGAGACCCAC TGCTACCA TGCACTGGAC 128 TCTACACACAC TCCCAAACAC TGCACACC TGCAAGCCT TCACACCACC TGCACCCC 128 TCTACACACCAC TGGAGACCAC ACCACCACC TGCACCCAGACC TGCACCCAGACC TGCACCCCAGACCACC TGCACCCCAGACCACC TGCACCCCAACCACC TGCACCCCACCC	301	TGCTTCGCGA	TGTACGGGCC	AGATATACGC	GTTGACATTG	ATTATTGACT	AGTTATTAAT
TRACGGTANA TGGCCGCCT TGGCCAATAG GGACTTTCC TACACGTCAA TAGGGTGGCCC TTGGCAGTAC TTGCCATATAGA TGCCCAATAGA GGACTTTCC TTCACATCAA TAGGCCCC TTGGCAGTAC TTCCCATATAGACCCC TTGGCAGTAC TTCCCATATAGACCCCC TACATCACCCCAC TGGCAGTAC TGCCCACTAC TGCCCACTAC TGCCCACTAC TGCCCCCCT TGCCACCCCACT TGACGTCAAT TGCCCACCCCAC	361	AGTAATCAAT	TACGGGGTCA	TTAGTTCATA	GCCCATATAT	GGAGTTCCGC	GTTACATAAC
TGACGTATAT TTACAGGTA AACTGCCCAC TEGCAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC TATTGACGT AACTGCCCAC TGACGAGTAC ATCAAGTGTA TCATATGCCA AGTACGCCCC TGTTTTGCCAC TGCATTTCC CAATGACGT AACTGCCCAC TGACGTCATACG TATTATGTCAA TGCCGATAC ATGACCTTAT CGTTTTTGCCAC TTACTGCCAG TGACGTCATATAGC TATTATGTCAC AGGGCGATTA TCCACCCCAT TGACGTCAAT GGGCGTGGAT AGCCGTTTTAC CCCAGTACA ATGACCTTAT TCAATTACAGC TATTACCCC CAATGACGC AAATGACCCC TGCATTACCC ATGGGGAGT TCAATTACAGC TCAATTACAC CAATGACCC AAATGACCCG TAGGCCTCTA CGGGGAGTGGAT TTAATACGCA TCACTATAGG CAACACTACAT GAGAACCCAC TGCATACACC AAATGACCGG TAGGCCTGCAAATCAACACTCCAAAATCAACCCC CACTCCCCACAA TCCACTTCCACGC CACTCCCCACAA TCCACTTCCACAACCCA AACAGGTCC CACTCCCCACAA TCCACTTCCACAACCCACACCCCACACCCCACCCCCACACCCCACAC	421	TTACGGTAAA	TGGCCCGCCT	GGCTGACCGC	CCAACGACCC	CCGCCCATTG	ACGTCAATAA
541 ATTTAGGGTA AACTGCCCAC TTGGCAGTAC ATCAAGTGTA TCCCACATAC AGTAGCCCC CATATGACGCT CAATGACGGT AATAGGCCCC CCTGGCAGTATA TGCCACATAC ATGACCTTAT GGTATTGCCA CATGACGGGA TACATCACC CCTGCGCAGTAC ATCACGGGA TTTCCAAGTC TCCACGGGA TCCACGGGA TAGGCCCCA TGCTACTGG CTTATGGAAG CAGGCCCTC TGCTACTG GGTGGGAGG CTCCTCTCTGT TGGAACCCC TCCTTCTTG TGGCACCCA ACAGGTGCC CACTCCCAGA TCCACTTGG CTTATGGAATC CTCACTATAGG AACAGGTGCC CACTCCCAGA TCCACTTGG GCAACTCGAC CACTCCAGA TCCACTTGG TGCAACCTC TGGAACCC AACAGGTGCC CACTCCCAGA TCCACTTGG GCAACTCGAC CACTCCAGA TCCACTTGG TGCAACCTC TGGAACCCC AACAGGTGCC CACTCCCAGA TCCACTTGG GCAACTCGAC CACTCCAGA ACAGGTGCC CACTCCCAGA TCCACTTGG GCAACTCGAC CACTCCAGA ACAGGTGCC CACTCCAGA TCCACTTGG AACACTCAACACT TGGAATCCA TGGAACCCC TGCACACCT TGGAACCCC TGCACACCT TGGAACCCC TGCCAACACC CACTCCAACACT TGGAACCCC TGCACACCT TGGAACCCC TGCCACACCT TGGAACCCC TGCCACACCT TGGAACCCC TGCCACACCT TGCAACACT TCCACTTATAC AGATAACCAA CCTCAAAAAT TCCAGGAAC CTCACACACAC CACAGGGCCCAC CACACCCCAA AGGACCCCAA CCTCACACACCAA AGCACCTCT CAGGCACCCC TCCCCCAACCC TCCACCAACCC TCCACCAACCC CACACCCCAA AGCACCCCAA CCTCACACCCAA AGCACCTCT CAGGCACCCC TCCCCCAACCC TCCACCCAAA CACACGGAACCCAA CCTCACACCAA AACACTCCAA CCTACACCCAA CCTCACACCCAA CCTCACACCCAA CCTCACACCCAA CCTCACACCCAA CCTCACCCAAA CACACGGAACCCAA CCCACACCCAA CCTCACCCAAA CACACGAACAC AAACACCAA CCCACACCCAA CCTCACCCAAA CCCACACCCAA CCCCACACCCAA CCCCCACACCCACCCC	481	TGACGTATGT	TCCCATAGTA	ACGCCAATAG	GGACTTTCCA	TTGACGTCAA	ТСССТССАСТ
CTATTGACGT CAATGACGGT AAATGGCCC CCTGGCATTA TGCCCAGTAC ATGACCTTAT GGGGACTTTCC TACTTGGCAG TACATCACC TATTAGTCA TGCCCAGTAC ATGACGATTACC 721 GGTTTTGGCA GTACATCAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC 721 TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTTGGCACCA AAATCAAGGG ACTTTCCAA 721 TCCACCCCAT TGACGTCAAT GGGAGTTTGT TTTTGGCACCA AAATCAAGGG ACTTTCCAA 721 TCTATATAAG CAACTCCGC CCATTGACGC AAAATCAAGGG TAGGCGTGTA CGGTGGGAGG 722 TCTATATAAG CAACTCCGC CACTTGACGA CATGACCACA TGCTTACTGG CTTATCGAAA 723 TCTATATAAGC CACACTATAGG GAGACCCAAC CTGCTACCA TGGACTAGGA 724 TCTATATACAGAC TCACTATAGG GAGACCCACA CTGCTCACCA TGGACTAGCA 725 TCTACTTTGG TGGCACCAC AACAGGTGC CACTCCCAGA TCCATTGGT GCAATCTGGA 726 TCTACTTTGG TGGCACCAC AACAGGTGC CACTCCCAGA TCCATTGGT GCAATCTGGA 727 TCTACACACTA CTGGAAATCA GAGGACCACAT AGGACTCCAC GAAGGGTTT TGGATTGGCA 727 TCTACACACTA CTGGAAATCA GTGGAATGCA TGAAGGATT CAAAGGATT TGAAGGATT 7201 GGCTGGATAA ACACCCACTC TGGAGTGCCA AAATTATGAA AAAATTATAA GAAACTACACACACT TGGAGTGGCA AAAATTATGAA AAAATTATAA GAGCACAAAA 721 TCTTTTCTTTTTTTTTTTTTTGGAAACCTC TGCCAACACT GCATATTATA AAAATTATAA CACCCAATAAT 7221 GAGGACACGG CTACGTATTT CTGTTGTGAA TCCGGGAATG GTAACATATAA 7221 GAGGACACGG CTACGTATTT CTGTTGTGAA TCCGGGAATG GTAACATATGA CCTGGCCTAC 723 TTTGCTTTCC CCCTGGCACC CTCCCCAAACC GTGACCTCTC GAGGACCACAC GGGCCCTGGC 7241 TTTGCTTTCC CCCTGGCACC CTCCCCAAACC GTGACCTCTC GAGGACCTCA CACGGGCCCTC 7241 TCCACTCCATC AGGACCACACACAA GTGCACCCC TCCACAACCC AAAGCTCT ACGGACCCTCAACC 7241 AGGGTTCTCG CCGGAAGCCA GGCCCCCCC CTCACACCC CAAGGACCCAC ACAGGGACCA 7241 AGGGTTCTCG CCGGAAGCCA GGCCCCCCC CTCACACCCC CAAACCCC 7241 CCCACTCCATC CTGGAAACCAA GTGCACCCC TCCCCCAAACCCC CACGACCCCCAAACCCC 7241 CCCACTCCATC CTGGAAACCAA GTGCACCCC TCCCCCCCC 7241 CCCACTCCATC CCCGGAAGACACAAAAAAAAATTTCCC CAAGGACCAC CAAGGACCACA 7241 TCCACTCCCT CAGCCCGGAAGA GCCCTGCCC TCCCCCCCC 7241 CCCACTCCATC CCCGGAAGACCAAAAACCACACCCCCAAAACCC CCAAACCCC 7241 CCCACTCCATC CCCGGAAGACCAAAACCACACCCCCAAAACCC CCAAACCCC 7241 CCCACTCCATC CCCGGAAGACCAAAAACCACAGGC CCCCAAACCCC 7241 CCCACTCCACCC CAAACCCAAAACCACCCCC CCCACACACCACC	541	ATTTACGGTA	AACTGCCCAC	TTGGCAGTAC	ATCAAGTGTA	TCATATGCCA	AGTACGCCCC
GGGACTITICC TACTIGGCAG TACATCTACG TATTAGTCAT CGCTATTACC ATGGTGATCC TOTAL STATEMENT TRACACCA ATGCTGATC TCACCCCAT TGACGTCAAT GGGCATGAT TTTGGCACCA AAATCAACCG TCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA AAATCAACCG GACTTTCCAAGTC TCATATATAG AATGTCGTAA CAAACTCCGCC CCATTGACGC AAATGAGCCGC TGAGGCTGTAC CGGTGGGAGA TTAATACGAC TCACTATAGG GAGACCCAAG CTTGGTAACCA TGGACTGGAC	601	CTATTGACGT	CAATGACGGT	AAATGGCCCG	CCTGGCATTA	TGCCCAGTAC	ATCACCTTAT
GTTTTIGGCA GTACATCAT GGGCGTGGAT AGCGGTTTGA CTCACGGGGA TTTCCAAGTC CCACCCCAT TGACGTCAAT GGGATTTGT TTTGGCACCA AAATCAACGG GACTTTCCAA AATGTCGTAA CAACTCCGCC CCATTGACGC AAATGGGCGG TAGGGGTGTA CGGTGGAGG TCTATATAAG CAGGCTCTC TGGCTAACTA GAGAACCCAC TGCTTACTGG CTTATGGAAA CTTAATATAAG CAGAGCCACC CACTGCACAG CTTGGTACCA TGGACTGGGAC TAGATACGAC TCACTATAGG GAGACCCACG CTCGCAGAATC CCTGAGCTGA AAACGCCACC CACTCCCAGA TCCATTGGT GCATTGGAA CCTGAGCTGA AGAGCCTGG AGAGCACGC CACTCCCAGA TCCAGTTGGT GCAATCTGGA TTTCACAACTA CTGGAATGCA GAGGACCACGC CACTCCCAGA TCCAGTTGGT GCAATCTGGA CCTGAGAATA CACCCCACTC TGGAGTGCCA AGAGGTTT GAAGGGTTT GAAGGGTTT CACACCTA ACACCCACTC TGGAGTGCCA AAATATGTAG AGAGGTTT GAAGGGTTT CACACCTA ACACCCACTC TGGAGTGCCA AAATATGTAG AGAGTTCAA GGGACGGTTT CAGGAGCACGG CTACCTTTT TGGAAACCTC TGCCAACACT GCATATTTAC AGATCAACAC CCTCGACATA CTTGGTCTTCC CCCGGCCAGG GACACTGGTC ACATGTTTCC CACCCACACC CACCCCACACCCT CCCCCAACCC GTGACCCTC CACCCCACACC CACCCCCACACCCT CCCCCACACC GTGACCCCT CACCACCCC AGACCCTC CACCCCCCACCCC CCACCCCC CCCCACCCC GTGCCCCCCCCC CACCCCCCACCCC CCCACCCCC CCCACCCCCCCC		GGGACTTTCC	TACTTECCAC	TACATCTACG	TATTACTION	CCCMAMMACC	ATCACCITAT
781 TCACCCCAT TGACGTCAAT GGGAGTTTGT TTTGGCACCA AAATCAACGG GACTTTCCAA AATGTCCTAA CAACTCCGCC CCATTGACGC AAATGGCCGG TAGGCGTGTA CCGTGGGAGG TCTATATAAG CAAGCCTCT TGGCTAACTA GAGAACCCAC TGCTTACTGG CTTATCGAAA TTAATACGAC TCACTATAGG GAGACCCAAC CTTGGTACCA TGGACTGGAC		GGTTTTTGGCA	GTACATCA AT	GGGCGTGGAT	ACCCCMMMCA	CTCACCCCCA	MUMBERS & CARC
AATGGCGTAA CAACTCCGCC CCATTGACGA AATGGGCGG TAGGCGTATA CGGAGGAGG TTAATATAAG CAGAGCTCTT TGGCTAACTA GAGAACCCAC TGCTTACTGGAA TTAATACGAC TCACTATAGG GAGACCCAAG CTTGGTTACCA TGGACATCT TGGCTAGCTAGG TGGCAGAGCC CACTCCCAGA TCGACTTGGT CCATTGGTACA TTAATACGAC TGGCAGAGC AACAGGTGCC CACTCCCAGA TCGACTTGGT GCAAGCTCGAC LTCTTCTTGG TGGCAGAGCA AACAGGTGCC CACTCCCAGA TCGAGGTTGT GCAATCTGGA TCCACTATAGG AGAACCCTG AGAGACACGT AGAGTTCCT GCAAGGCTTC TGGGTAGCC TTCACACTA CTGGAATGCA GTGGGTGCA GAGACCCACT GCAAGTCCAGG GAAAGGGTTT GAAGTGGATT L201 GGCTGGATAA ACACCCACTC TGGAGTGCCA AAATAGTGAA GAGACACTT L201 GGCTGGATAA ACACCCACTC TGCAAGACCT GCAAATATTACA AGATAACCAA CCTCAAAAAT L213 GAGGACACGG CTACGTATT CTGTGTGAGA TCCAGGTATTACA CATTAACCAA CCTCAAAAAT L321 GAGGACACGG CTACGTATT CTGTGTGAGA TCCAGGTATTACA CATTAACCAA CCTCAAAAAT L321 GAGGACACGG CTACGTATT CTGTGTGAGA TCCAGGCACCAC CAAGGGCCCAC L331 TTTGCTTACT GGGCCAAGG GACACTGGT CACGTCTTC CAGCTACCAC CAAGGGCCCAC L441 TCGGTGTCC CCCGGCAGG GACACTGGT CTACAGTCCT CAGGCACCAC CAGGGCCCTG L501 TGCCTGGTCA AGGACCACT CCCGGACCG GTGACCGTGT CAGGCCCTC CAGGACCCT CAGGACCCT CAGGACCCT CAGGACCCT CAGGACCCT CAGGACCCT CAGGACCCT CAGGACCCT CAGGACCCAGAC CTCACACCT CAGGACCACACCT CAGGACCCAG CACACCCT CAGGACCAGAC CACACCCT CAGGACCAGAC CACACCCT CAGGACCAGAC CACACCCT CAGGACCAGAC CACACCCACACCT CAGGACCAGAC CACACCCACACCT CAGGACCAGAC CACACCCACACCT CAGGACCAGAC CACACCCACACACACCACAC		TCCACCCCAT	TCACCTCAAT	CCCACMMMCM	MUMCCCACCA	CICACGGGA	CLOCKAGIC
901 TTANTACAC TCACTATAGG GAGACCCAAG CTTGGTACCA TGGACTGGAC		AATCTCCTAA	CAACTCCCCC	CCAMMCACCC	ANAMOGGACCA	MAATCAACGG	GACTITCCAA
TRANTACGAC TCACTATAGG GACACCAAG CTTGGTACCA TGGACTGGAC		TOTATA	CARCICCECC	CCATIGACGC	AAATGGGCGG	TAGGCGTGTA	CGGTGGGAGG
1081 CCTGTAGGTGA AGAAGCCTG AGAGCAGC CACTCCCAGA TCCAGTTGGT GCAATCTGA 1141 TTCACAACTA CTGGAATGCA GTGGGTGCAA AGAAGCCTC AGAATGCTC TGCAAGGCTTC TGGGATTGCT 1201 GGCTGGATAA ACACCCACTC TGGAGTGCCA AAAATATGTAG AGACTTCAA GGGACGGTTT 1201 GGCTGGATAA ACACCCACTC TGGAGTGCCA AAAATATGTAG AGACTTCAA GGGACGGTTT 1201 GGCTGGATAA ACACCCACTC TGGAGTGCCA AAAATATGTAG AGACTTCAA GGGACGGTTT 1201 GAGGACACGG CTACGTTATTT CTGTGTGAGA TCCGGGAATG GTAACATATCA CCTGGCCTAC 1321 GAGGACACGG CTACGTATTT CTGTGTGAGA TCCGGGAATG GTAACATATCA CCTGGCCTAC 1321 TTTGCTTACT GGGGCCAAGG GACACTGGTC ACGGCCCTG CAGCTACCCCAAGC CCCTGGCCCC CCCTGGCACC CTCCTCCAAG AGCACCTCT GAGGCACCAGC GGCCCTGGCC 1501 TGCCTGGTCA AGGACTACTT CCCCGGAACC GTGACGCTTC GAGGCACCAGC GGCCCTGGCC 1501 TGCCTGGTCA AGGACTACTT CCCCGGAACC GTGACGCTTC GAGGCCCCTG 1501 TGCCTGGTCA CGCTCCCCC CAGCACCTT CTCAAGTCCT CAGGGACCTCA AGCGCCCTG 1501 TGCCTGGTCA CGCTCCCCC CAGCACCTT CTCAAGTCCT CAGGGACCTA CTCCCTCAGC 1501 TGCCTGGTCA CGCTCCCCC CAGCACCTT CTCAAGTCCT CAGGACCTCA CCTACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACAA GGTGGACAGA AAAGTTGGTG AGAGGCCAC ACAGGGAGG 1741 AGGGTTGTG CTGGAAGCA GAGGCCCGT CTCTCCCCG ACGCCCAAA CCTACATCTG CAACGTGAAG 1801 CCCAGTCCAG GCCACAGG CAGGCCCGT CTGCCCTCTC AGGGCCACG CCTACATCCAGC 1801 CCCAGTCCAG GCCACAGG CAGGCCCGT CTGCCCTCTC CAGGCCCCAA ACGCCCAAA ACCCTACATCAT CTCACACCCCAA ACCCCCAAA ACCCTACACCCAA ACCCTACACCCCAA ACCCCCCAAA ACCCTACACCCCAA ACCCCCCAAAACC CAAAGGGGCA GCCCTGCCCC TGACCCCAAAACC CAAGGACACC CCCAAACCCCAAA GCCCAAAACC CAAGACCACACCCAAAACC CAAGACACCACACCCCAAAACC CAAGACCACACCCCAAAACC CAAGACCACACCCCC TGACCCAAAACC CAAGACACCCCC CCCAAAACC CCCAAAACC CAAGACCACCCCAAAACC CAAGACACC CCCAAAACC CAAGACCACCCCAAAACC CAAGACCACCCCAAAACC CAAGACCACCCCAAAACC CAAAACCAAACC CAAAACCAAACC CAAAACCAAACC CAAAACCAAACC CAAAACCAAACC CAAAACCAAACC CAAAACCAAACC CAAAACCAAACC CACCCCAAAACC CAAAACCAAACC CAAAACCAAACC CACCCCAAAACC CAAAACCAAACC CACCCCAAAACC CACCCCACCCCCACCCCCACCCCCACCCCCACCCCCACCCC		TCIMIMIAAG	CAGAGCICIC	CACACCCAACTA	GAGAACCCAC	TGCTTACTGG	CTTATCGAAA
1081 CCTGAGCTGA AGAAGCCTGG AGAGCAGTC AGGATCTCCT GCAAGGCTTC TGGGTATGCC 1141 TTCACAACTA CTGGAATGCA GTGGTGCAA GAGATGCCAG GAAAGGGTTT GAAGTGGATT 1261 GGCTTGATA ACACCCACTC TGGAGTGCCA AAAATATGTAG AAGACCTCAAA AGACCCACTC TGGAACCCT GCAACACT GCATATTTAC AGATAACATCA CCTGGCCTAC 1321 GAGGACACGG CTACGTATTT CTGTGTGAGA TCCGGGAATG GTAACCTATGA CCTGGCCTCA 1381 TTTGCTTACT GGGGCCAAGG GACACTGGTC ACTGTCTCTG CAGCTACCAC CAAGGGCCCCA 1441 TCGGTCTCC CCCCGCACCC CTCCTCAAG AGCACCTCTG GGGCCACAC GGCCCTGGC 1501 TGCCTGGTCA AGACTACTT CCCCGGACCG GTGACGGTT CGTGGAACTC AGGCCCCCTG 1501 ACCAAGGGCC TGCACACCT CCCCGAACCC GTGACGGTC CAGGACCCC AGGCCCCTGGC 1501 ACCAAGGCCCA GCAACACCTT CCCGGACCG GTGACGGTT CGTGGAACTC AGGCCCCCTG 1621 AGCGTGGTGA CCGTGCCCT CAGCAGCTTG GCCACCCAGA CCTACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACCAA GGTGGACACA AAAGTTGGTG AGAGGCCACA CAAGGGCACAC 1501 CCCAGTCCAG GCAACACCAA GGTCACACGC TCTCTCCCAGC 1801 CCCAGTCCAG GCACACACG GCTCACACGCC TCTCGCCCGC 1801 CCCACTCATG CTCAAGCCAG GCTCACACCCG CTCTCCCCGC 1801 CCCACTCATG CTCAAGCCAG GCCCCACACGCC TCTCCCCCC CAGCACCCCAC ACCGGGACGC 1801 CCCACTCATG CTCAAGCCAG GCCCCTGCCC TGACCCTAG CCCACCCCAC		CTCTTTATACGAC	TCACTATAGG	GAGACCCAAG	CITGGTACCA	TGGACTGGAC	CTGGAGAATC
1201 GCTGGATAA ACACCACTC TGGATGCCA AAATATGTAG AAGACTTCAA GGGAACTT 1201 GCCTTCTTT TGGAAACCTC TGCCACACAT GCATATTTAC AGATTACAA CCTCAAAAAT 1321 GAGGACACG CTACGTATTT CTGTGTGAGA TCCGGGATG GTAACTATGA 1381 TTTGCTTACT GGGGCCAAGG GACACTGGTC ACTGTCTCT CAGCTACACC CAAGGGCCCA 1381 TTGCTTACT GGGGCCAAGG GACACTGGTC ACTGTCTCT CAGCTACAC CAAGGGCCCA 1381 TCGGTCTTC CCCTGGCACC CTCCTCCAAG ACACCTCTG GGGCCACAC GGCCCTGGCC 1501 TGCCTGGTAA AGGACTACTT CCCGGAACCG GTGACGTCT CAGGACTCT CAGGACTCAC 1561 ACCAGCGGC TGCACACCTT CCCGGCTGC CTACAGTCCT CAGGACCTC CAGGACCTAC 1561 ACCAGCGCC TGCACACCAC GCCACACCAC GCCACACCAC CCACACCTC CAGCACTCT CAGCACCTAC CAGCACCTAC CAACACCAC GCACACCACA GCCACACCACA		CTCTTCTTGG	TGGCAGCAGC	AACAGGTGCC	CACTCCCAGA	TCCAGTTGGT	GCAATCTGGA
1261 GCCTGGATAA ACACCACTC TGGAGTGCCA ANATATGTAG AAGACTACAA GGGACGGTTT 1261 GCCTTCTCTT TGGAAACCTC TGCCAACACT GCATATTTAC AGATAAGCAA CCTCAAAAAT 1321 GAGGACACGG CTACGTATTT CTGTGTGAGA TCCGGGAATG GTAACTATGA CCTGCAACACT 1381 TTTGCTTACT GGGGCCAAGG GACACTGGTC ACTGTCTCTG CAGCTAGCAC CAAGGGCCCA 1441 TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCAACCA AGGGCCCAGG 1501 TGCCTGGTCA AGGACTACTT CCCCGAACCC GTACGGGTG CGTGGAACTC AGGCGCCCTG 1501 TGCCTGGTCA AGGACTACTT CCCCGAACCC GTACAGGTCT CAGGACTCA AGGCCCCTG 1501 ACCAGCGCG TGCACACCCAA GGTGGAACTC CAGGACTCA CCTACATCTG 1501 ACCAGCCCA GCAACACCAA GGTGGACACA AAAGTTGGTG ACCACACACCAA GCAGCCCTG 1621 AGCGTGTCT CTGGAAGCCA GGTCCACACACAA GAGGCCCAGA CCTACATCTG CACACTGAAT 1681 CACAAGCCCA GCAACACCAA GGTGGACACA AAAGTTGGTG ACCGACCCCAGA CCCACACACCAA GGTGGACACA AAAGTTGGTG ACCGACCCCAG GCTATCCAGC 1801 CCCACTCATG CTGGAAGCCA GGCTCAGCCC TCCTCCCCG ACCGCTCCG GCTATCCAGC 1801 CCCACTCATG CTCAGGGAG GGCCCCTTCTCC CCAGCTCTTC CAGGCACCAG 1921 GCTAGGTGCC CTAACCCAG GCCCTGCACA CAAAGGGGC CTCTGCCCG 1861 CACAACCCA ACCCCAG CCCTGCACA CAAAGGGGC CCCACCCCCAA 1981 CAAGAGCCAT ATCCGGGAG ACCTTCTCTC CTCCCAGATT CCAGGACACC 1981 CACACCCCC CAGCCCGGAC ACCTTCTCTC CTCCCAGATT CCAGTAACCC CCACCCCCAA 101 TCCACCCCC CAGCCCGGAC ACCTTCTCTC CTCCCAGATT CCAGTAACCC CCACCCTCAC 1981 CAGCACAGC CCACACACCAA CCTTCTCTC CTCCCAGATT CCAGTAACCC CCACCCTCAC 1981 CAGCACAGC CCACACCTCAA CCTTCTCTC CCCAGATT CCAGTAACCC CCACCCTCAC CCACATCTCT 101 CTCTGCAGAG CCAAATCTT GTGACAAAAC TCACACATGC CCACCCTGAC CCACCTGAC 101 CTCTGCAGAG CCAAATCTT GTGACAAAAC TCACACATGC CCACCCTGAC CCACGTGAC 101 AGCCCCAGG CCCACACTCT TCCTCTTCC CCCCAAATCT CCACCACATCC CCACCTGAC CCACCTGAC 101 AGCCCCAGG ACCGTCAGT TCCTCTTCC CCCCAAAACC CCACCCTCAC CCACCTGAC 101 AGCCCCAGG ACCGTCAGT TCCTCTTCC CCCCAAAACC CCCCCCAAACC CCACCTGAC 101 AGCCCCAGA ACCGTGAC CGTGGGGG TGCACAACC CCACCTGAC CCACCTGAC 101 AGCCCCAGA ACCGTGAC GCTGGGGG TGCACACAACC CCCCCACACC CCCCACACCC CCCCACACCC CCCCACCCCCC		CCTGAGCTGA	AGAAGCCTGG	AGAGACAGTC	AGGATCTCCT	GCAAGGCTTC	TGGGTATGCC
1321 GAGGACAGG CTACGTATTT CTGTGTGGAA TCCGGGAATG GTAACATATGA CCTGAAAAT 1321 GAGGACAGG CTACGTATTT CTGTGTGGAA TCCGGGAATG GTAACATATGA CCTGGCCTAC 1381 TTTGCTTACT GGGGCCAAGG GACACTGGTC ACTGTCTTC CAGCTAGCAC CAAGGGCCCA 1441 TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGCACAGC GGCCCTGGGC 1501 TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTCT CGTGGAACTC AGGGCCCTG 1561 ACCAGCGGCG TGCACACCTT CCCGGACCG CTACAGTCCT CAGGACTCTA CTCCCTCAGC 1621 AGCGTGGTCA CCGTGCCCCT CAGCACCTTG GGCACCCCCCAC CCTACAGTCTA CTCCCTCAGC 1681 CACAAGCCCA GCACACCAA GGTGGACCAG CCTACACTCTG CAACGTGAAT 1681 CACAAGCCCA GCCACACCAA GGTCACACG CTCCTGCTG ACGCATCCCG GCTATCCAGC 1801 CCCAGTCCAG GCCACACCAA GGTCACCCC TCCTGCCTG ACGCATCCCG GCTATCCAGC 1801 CCCAGTCCAG CTCAAGACCAA GGCTCACCC CTGCCTCTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAAGGCAA GCCCTGCACA CAAAGGGGAA GCCTTACAGCC 1981 CAAGAGCCAT ATCCGGGAGA ACCCTGCACA CAAAAGGGGA GGTGCTGGC CTCAGACCCA 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA ACCCCCAAA GGCCAAACTC 1981 CAAGAGCCAT ATCCGGGAGA ACCCTGCCCC TGCCCCCC CCACCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGCCTCGA ACCTTCTCTC CTCCAGATT CCAGTAACCC CCAACCCCAAA GCCCAAACTC 2101 CTCTGCAGGG CCCCAAATCTT GTGACAAAAC TCACCACATGC CCACCCCAAA GGCCAAACTC 2221 GGGACAGGCC CCGCCCTCCA GCTCAAGGCG GCACAGGTGC CCTGCACCC 2221 GGGACAGCC TCGCCCTCCA GCTCAAGACC CCACCGTGCC CAGCTGAACC 2221 GGGACAGCC TGGCCCTCCA GCTCAAGCC CCACCGTGCC CAGGTAAGCC 2231 TCCTGGGGG ACCGTTGACA TCCCTCTCC CCCCAAAACC CCAAGGACACC CTCATGACC 2401 AGTTCAACTG GTACCTGCAC CCTGGAGG TGCACACAC CCAACAAAC CCACCCCAAC CCACCCCAAC CCACCCCAAC CCACCCCAAC CCACCCCCAC CCCCCC		TTCACAACTA	CTGGAATGCA	GTGGGTGCAA	GAGATGCCAG	GAAAGGGTTT	GAAGTGGATT
1381 TTTGCTTACT GGGGCAAGG GAACTTGTTGTGAGA TCCGGGAATG GTAACTATGA CCTAGGCCCA 1441 TCGGTCTTCC CCCTGGCACC CTCCTCCAAG AGCACCTCTG GGGGCACAGC GGCCCTGGGC 1501 TGCCTGGTCA AGGACCTCT CCCGGAACCG GTGACGTGTC CTGCGCACCG 1561 ACCAGCGGG TGCACACCTT CCCGGACCG GTGACGTCT CAGGGACTCTA CTCCCTCAGC 1561 ACCAGCGGG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCCTCAGC 1561 ACCAGCGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCCTCAGC 1561 ACCAGCGCG GCACACCCTA GGTGGACACA CATACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACCAA GGTGGACAAG AAAGTTGGTG AGAGGCCAGC ACAGGAGGG 1741 AGGGTGTCTG CTGGAAGCCA GGCTCAGCCC TCCTCCTCA ACCCGGAGGG 1801 CCCAGTCCAG GGCAAGCA CAGCCCCTT CTGCCTCTG ACGCATCCCG GCTATGCAGC 1801 CCCAGTCCAG GGCAAGCA CAGCCCCTT CTCCCCGC 1861 CCCACTCATG CTCAGGGAGA GGGTCTTCTG GCTTTTTCCC CAGGCATCCG GCTAGCACG 1921 GCTAGGTGCC CCTAACCCAG GCCCTCCAC CAAAGGGGCA GGTCTGGCC 1981 CAAGAGCCAT ATCCGGGAGA ACCCTGCCCC TGACCTCAAG GGCACCCCAAA 1921 TCCACTCCCT CAGCCAGA ACCTTCTCTC CTCCCAGATT CCAGTCACTC CAACCTCCC 1981 CACACTCCCT CAGCCCAGA ACCTTCTCTC CTCCCAGATT CCAGTCACTC CAACCTCCC 2041 TCCACTCCCT CAGCCCAGA ACCTTCTCTC CTCCCAGATT CCAGTAACTC CCAATCTTCT 2101 CTCTGCAGG CCCAAATCTT GTGACAAAAC TCACCACTCC CCACCCCAAA GGCCAAACCC 2221 GGGACAGGC CCCACACCTCA GCTCAACGC CCACCCCAAA CCCCAAACCC 2221 GGGACAGGC CCCACACCCCA GCTCAACGC CCACCCCAAACCC CAAGCACACC 2221 GGGACAGCC CTGAGCAGC CCTCAAGCCC CCACCCTCAA CCCCCAAACCC 22341 CCCGGGGC CCAGCCCGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTCAAC 2241 AGCAGTACAA CAGCCTACA TGCGTGGTC CCCCACAAACC CCAAGGACAAC CCTCATGACC 2341 CCCGGACCCC TGAGGTCAC GGGTGGAGG TGCATAATGC CCACCGAAGAC CCTCATGACC 2341 CCCGGACCCC TGAGGTCA CGTGGTCA CCTCTCTCTC CCCCAAAACC CAACCTCAC CAACCTCAC 2401 AGCAGTACAA CAGCACAAG TGCGTGGTC CCCCAAAACC CAACCTCCAC CACCTCAACC 2401 AGCAGTACAA CAGCACAAG TGCGTGGTC CCCCAAAACC CAACCTCCAC CACCCTCACC CAACCTCAC CAACCTCAC CAACCTCCAC	1201	GGCTGGATAA	ACACCCACTC	TGGAGTGCCA	<u>AAATATGTAG</u>	<u> AAGACTTCAA</u>	GGGACGGTTT
1381 TTTGCTTACT GGGCCAAGG GACACTGGTC ACTGTCTCTC CAGCTACAC CAAGGGCCCA 1441 TCGGTTTCC CCTGGCACC CTCCTCCAAG AGCACCTCTG GGGCACAGC GGCCCTGGGC 1501 TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCTG 1501 ACCAGCGGC TGCACACCTT CCCCGAACCG GTGACGGTGT CGTGGAACTC AGGCGCCTG 1521 AGCGTGGTGA CCGTGCCCT CAGCACCTG GGCACCAGC CAAGGTGAT 1681 CACAAGCCCA GCAACACCAA GGTGGACAAG AAAGTTTGGT AGAGGCCAGC ACAGGAAGT 1741 AGGGTGTCT CTGGAAGCCA GGCCCCGT CTCTGCCTGG ACGCATCCCG GCTATGCAGC 1801 CCCAGTCCAG GGCAGCAAGG CAGGCCCCGT CTGCCTGG ACGCATCCCG GCTATGCAGC 1801 CCCAGTCCAG GCCAGACAGG CAGGCCCCGT CTGCCTCTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAAGCCAG GGCCCCTTC CTGCCTCTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAAGCCAG GCCCTGCACA CAAAGGGGCA GGTGCTTGG GCAGCACAG 1921 GCTAGGTGCC CTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTTGG GCAGCACAG 1921 CCAGTCCCT CAGCTCGGAC ACCCTGCACA CAAAGGGGCA GGTGCTTGG CCAACCTGC 2041 TCCACTCCCT CAGCTCGGAC ACCCTTCCCC CTGCACCAAACCC CCACCCCAAA GGCCAAACTC 2161 AGCCCAGAGC CCCAAAACCTT GTGACAAAAC TCACACATGC CCACCCCAAA GCCCAAAACCC 2161 AGCCCAGGC CCCACCCCTCA GCTCAAGGCG GGACAGGTGC CCACCCCTAA CCTGCATCA 2221 GGGACAGGC CCCAGCCGGGT GCTGACACGT CCCCCCAAAACC CAAGGACAC CTGCATCA 2221 GGGACAGGC CCAGCCGGGT GCTGACACGT CCCCCCAAAACC CAAGGACAC CTGCATCA 2401 AGTTCAACTG GTACGTGACA TGCCTGGTGG TGGACTAAGC CAAGGACAC CTCATGATCT 2341 CCCGGACCC TGAGGTCACA TGCGTGGTG TGGACCTCAT CTCTTCCTCA GCACCTGAAC 2221 GGACAGGCC CAGCGGGT GCTGGAGG TGCATAAGC CAAGACAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGACA TGCGTGGTG TGGACTAAACC CAAGGACAC CTCATGATCT 2341 CCCGGACCCC TGAGGTCAC CGTGGTGGT TGCATAAGC CAAGACAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAC CGTGGGGGG TGCACAAAACC CAAGACAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAC CGTGGGGGG TGCACAAAACC CAAGACAC CCTGAGGGC 2521 TGAATGGCA GGAGTACAA GGCGTGGAG TGCATAAGC CAAGACAC CCTGAGGGC 2521 TGAATGGCA GGAGTACAA GGCGTGGAG TGCACAAAACC CAAGACAC CCTGCAGGGC 2521 TGAATGGCA GAACACACAGGT CCTGAGGGTC CCCCCCTCC CCGACCAC GGACAAAACC CCCACCATGGC 2521 TGAATGGCA GCCGTGAG GACAACAC CCCCCCTGCC GGGACACAC CCCCTTCCC CCACCAAAACC CCCCCCACCCC GGGACACAC GCGGGGGAC CTCCCCTGCC GGG	1261	GCCTTCTCTT	TGGAAACCTC	TGCCAACACT	GCATATTTAC	<u>AGATAAGCAA</u>	CCTCAAAAAT
1441 TGGTCTTCC CCCTGGCAC CTCCTCAG AGCACCTCTG GGGGCACAGC GGCCTGGGC 1501 TGCCTGGTCA AGGACTACTT CCCCGAACCG GTGACGGTCT CAGGACTC AGGCGCCTG 1561 ACCAGCGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCA AGGCGCCTG 1621 AGCGTGGTCA CCGTGCCCCC CAGCAGTTTG GGCACCCAGA CCTTACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACAA GGTGGACAGA AAAGTTGGTG AGAGCCAGC ACAGGGAGGG 1741 AGGGTGTCTG CTGGAAAGCCA GGCTCAGCGC TCCTGCCTGG ACGAGCCAGC CTTGCCCGC 1861 CCCAGTCCAG GGCACAGG CAGGCCCGT CTGCCTCTTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAGGGAGA GGCTCTTCTG GCTTTTTCCC CAGGGTCTGG GCAGCACAG 1921 GCTAGGTGCC CTTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTCTGG CCAGCCAGC 1981 CAAGAGCCAT ATCCGGGAG ACCCTTCTCTC CAACGTAACC 2041 TCCACTCCCT CAGCTCGGAC ACCCTTCTCT CAGCCCCAAAACCC 2161 AGCCCAGGC CCCAAAATCTT GTGACAAAAC CTCCCAGGATC CCAACTTCTC 2101 CTCTGCAGG CCCAAAATCTT GTGACAAAAC CCCCCCAAA GGCCAAACCC 2221 GGGACAGGC CCAAAATCTT GTGACACAACC CCACCCTCCA CCCACCTCCAC 2221 GGGACAGGC CCAAAATCTT GTGACACACACTC CCACCTTCCCA 2221 GCGACAGGC CCAAGCCGGT CCTGCCCC TGACCCTCAT CCACCTTCCCA 2221 GCGACAGGC CCAGCCGGGT GCTGACACACTC CCCCAAAAAC CCTGCAGCC CAGGTAACCC 22341 CCCGGACCC TGAGCTCAT TCCCTCTTCC CCCCAAAACC CAACGACAC CTCATGATCT 2341 CCCGGACCC TGAGGTCAA TGCCTGGGC TGGACCTCAC CAAGACAAAC CCTGAGACA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGCATAATGC CAAGACAAAAC CCTGAGGTCA 2401 AGTTCAACTC CAAGCCAAA GGCGTGGAGG TGCATAATGC CAAGACAAAAC CCTGAGGTCA 2401 AGCCCGGA CCC TGAGGTCAC GGCGTGAGG TGCATAATGC CAAGACAAAAC CCTGAGGTCA 2401 AGCCCGGA CCC TGAGGTCAC GTGGGGAGG CCCCCACCACC CCCACCGAGA 2401 AGCCCCCC TGAGGCCC TGAGGTCAC GGCGTGAGG CCCCCACCACC CCCACCGAGA 2401 AGCCCCGAG AGCACGGA GGCGGAAGG CCCTGCCC CAAGACACC CTCATGAGAC 2401 AGCCCCGAG AGCACCGG GTGAGGC GGCGGGAGG TGCCCACCC CCCACCACCC CCCACCGCC CACCGAGAAAAC CCCCCACCCCCACCC CCCACCACCCCCCACCC CCCACCA		GAGGACACGG	CTACGTATTT	CTGTGTGAGA	TCCGGGAATG	<u>GTAACTATGA</u>	CCTGGCCTAC
1501 TGCCTGGTCA AGGACTACT CCCCGACCG GTGACGGTGT CAGGACTCT AGGCGCCTG 1561 ACCAGCGGCG TGCACACTT CCCCGCTGTC CTACAGTTCCT CAGGACTCTA CTCCCTCAGC 1621 AGCGTGGTGA CCGTGCCCT CAGCAGCTTG GGCACCCAGA CATCAGTTCT CAACGTCAGT 1681 CACAAGCCCA GCAACACCAA GGTGGACAAG AAAGTTGGTG AGAGGCCAGC ACAGGGAGGG 1741 AGGGTGTCTG CTGGAAGCCA GGCTCAGCGC TCCTGCCTGG ACGCATCCG GCTATGCAGC 1801 CCCACTCAGG GGCAGCAAGG CAGGCCCCGT CTGCCTCTTC ACGCATCCG GCAGCACAGG 1801 CCCACTCATG CTCAGGGAGA GGGTCTTCTG GCTTTTTCC CAGGCTCTGG CCAGGCACAG 1921 GCTAGGTGC CTCAGGGAGA ACCCTGCCC TGCCTCTTC ACGCCTCTGG 1981 CAAGAGCCAT ATCCGGGAGA ACCCTGCCCC TGACCTAAGC CCACCCCAAA GGCCAACCTC 2041 TCCACTCCCT CAGCTCGGA ACCCTGCCC TGACCTAAGC CCAACCCCAAA GGCCAAACTC 2101 CTCTGCAGGA CCCAAATCTT GTGACAAAAC TCACACATG CCACCGTGC CAGGTAAGCC 2161 AGCCCAGGC TCGCCCTCA GCTCAAGGCG GCACAGTGC CCAAGCACAC 2221 GGGACAGGC CCCACCCTCA GCTCAAGGCG GCACAGTGC CCACCTCCA 2221 GGGACAGGC TCGCCCTCA GCTCAAGGCG GCACAGTGC CCACCTCCA 2221 GCGACCCC TGAGCTCAC TCCCTCTCC CCCCAAAACC CCACGTGCC CAGGTAAGCC 22341 CCCGGGCC TCGCCCTCA GCTCAAGCG GCACAGTGC CCACCTCCA 2401 AGTTCAACTG GTACGTGGA TCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2440 AGTTCAACTG GTACGTGGA GGGGTGGAG CCTGAGAGAC CCTGAGGTCC 2451 TGAAGTACAA CAGCACAA GGGGGTGGAG TGCAAAAAG CAAGGACAAC CCTGAGGTC 2461 AGCAGTACAA CAGCACAA GGGGGTGGAG TCCAACAAAGC CAAGAAAAG CCGGGGGAG 2461 AGCAGTACAA CAGCACAA GGGGTGGAG TCCAACAAAGC CAAGAAAAA CCGGGGGAG 2461 AGCAGTACAA CAGCACAA GGTGGGCC CCCAACAAAGC CAAGAAAAA CCGGGGGAG 2461 AGCAGTACAA CAGCACAA GGTGGGACC CCCAACAAAAC CAACAAAAC CAACAAAAC CAACAA		TTTGCTTACT	GGGGCCAAGG	GACACTGGTC	ACTGTCTCTG	<u>CA</u> GCTAGCAC	CAAGGGCCCA
1561 ACCAGCGGCG TGCACACCTT CCCGGCTGTC CTACAGTCCT CAGGACTCTA CTCCCTCAGC 1621 AGCGTGGTGA CCGTGCCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACAA GGTGGACAAG AAAGTTGGTG AGAGGCCAGC ACAGGGAGGG 1741 AGGGTGCTCG CTGGAAGCCA GGCTCAGCCC TCCTGCCTCG ACGCATCCCG GCTATGCAGC 1801 CCCAGTCCAG GGCAGCAAGG CAGGCCCCGT CTGCCTCTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAGGGAGA GGGTCTTCTG GCTTTTCCC CAGGCTCTGG GCAGGCACAG 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTGGC TCAGACCTGC 1981 CAAGAGCCAT ATCCGGGAGA ACCCTTCCTC CTCCCAGATT CCACCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGGCTCGACA ACCCTTCTCTC CTCCCAGATT CCACGTAACCT CCAATCTTCT 2101 CTCTGCAGAG CCCAAATCTT GTGACAAAC TCACACATGC CCACCCCAAA GGCCAAACCC 2221 GGGACAGGC CCCAAATCTT GTGACACAT CCACCTCCAT CTCTTCCCA 2221 GCGACAGCC CCAGCCGGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAAC 2221 CCCGGACCC TGAGGTCAA TGCCTGTGGTG TGCACAGAC CCTCATGATCT 2341 CCCGGACCC TGAGGTCAA TGCCTGTGGTG TGCACAGAC CCTCATGATCT 2341 CCCGGACCC TGAGGTCAA TGCCTGGTGG TGCACAGA CCTCCATCCAT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGCATAACC CAAGGACAC CTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGCATAAACC CAAGGACAC CTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAG TGCATAATGC CAACCAAAC CAAGGACAC CTCATGATCT 2401 AGCTCAACAA CAGCACGTAC CGTGTGGTG TGCACAAAC CAAGGACAC CTCATGATCT 2401 AGCTCACCC TGAGGTCAA GGCGTGGAGG TGCATAAACC CAACCAAAG CCCTGAGGGC 2401 AGCACGTCC CAAAGCCAAA GGCGCGGAGG TGCATAAACC CAAGGACAAC CCCCCAGAGAC 2401 AGCACGACA GGGGACAAA GGCGCGAAGC CCCCAAAACC CCCCCAACAAAC CAAGGACAAAC CAAGGACAAAC CAAGGCCAAA GGCACAAAC CAAAGGCCAAA GGCACAAAC CAAAGGCCAAA GGCACAAAC CAAAGGCC CCCAACAAAC CAAAGACAAAC CAAAGACAAAC CAAAGACAAAC CAAAGACAAAC CAAAGACAAAC CAAAGACAAC CAAAGACAAC CAAAGACAAC CAAACCAAGAC CAACCTCGC CAAAACCAAGC CAACCTCGC CAAAACCAAG CAACCAAACAAC CAACCAAGAC CAACCAAGAC CAACCAAGAC CAACCAAGAC CAACCAAGAC CAACCAAC	1441	TCGGTCTTCC	CCCTGGCACC	CTCCTCCAAG	AGCACCTCTG	GGGGCACAGC	GGCCCTGGGC
1621 AGCGTGGTGA CCGTGCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACCAA GGTGGACAGA 1741 AGGGTGTCTG CTGGAAGCCA GGCTCAGCGC 1801 CCCAGTCCAG GGCAGCAAGG CAGGCCCGT TCCTGCCTGG ACCGATCCCG GCTATGCCCGC 1861 CCCACTCATG CTCAGGGAGA GGGTCTTCTG CTGCCTCGT CAGGCTCTGC CGC 1861 CCCACTCATG CTCAGGGAGA GGCTCTCTG CCTGCCTCTC CAGGCTCTGG GCAGCCAGG 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTGGG CCACCCCAAA GGCCAAACTC 1981 CAAGAGCCAT ATCCGGGAG ACCTTCTCC CTGCCTCTC CCAGCCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGCCCGGAC ACCTTCTCC CTCCCAGATT CCAGTAACTC CCACCCCAAA GGCCAAACTC 2041 TCCACTGCAG CCCAAATCTT GTGACAAAAC CCACCCTAAC CCACCCCAAA GCCCAAACTC 2161 AGCCCAGGCC TCGCCCTCCA GCTCAAGGCG GGACAGGCC CCACCCTGCC 2281 TCCTGGGGG ACCGTCAGT CTCCCAGAACC CCACCCTCAC CCCACAAACC CCACCTCAC CCCCAAAACC CCACCCTGAC 2281 TCCTGGGGG ACCGTCAGT TCCCTCTCC CCCCAAAACC CCACGAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAC TCCCTCTCTC CCCCAAAACC CAAGACACC CTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG CCCACGAGAC CCTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG CCCACCAAAACC CAAGACACAC CCCCAAAACC CCCCAAAACC CAAGACACC CTCATGAGTCA 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGGACCCC TGAGGTCAA 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGGACCCC TGAGGTCAC CCCCAAAACC CAAGACACAC CCCCAAGGGC 2461 AGCAGTACAA CAGCCAAA GGCGGTGGAG CCCCCAAAACC CCACCTGGC CCCATGAGGC 2461 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCAACAAACC CCCCAAGACC CCCCAAGGGC 2521 TGAATGGCA GGAGACACAC CCCCAAAACC CAAGACACAC CCCCAAGGGC 2641 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCCCAAAACC CCCCAAGAGC CCCCATCGAGGC 2641 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCCCAAAACC CCCCAAGAGC CCCCATCGAGGC 2641 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCCCCATCCC GGGCACAT GGACCACAT GGACCACACT GGACCACAT GGACCACAT GGACCACAT GGACCACAT GGACCACACACACACACACACACACACACACACACACAC	1501	TGCCTGGTCA	AGGACTACTT	CCCCGAACCG	GTGACGGTGT	CGTGGAACTC	AGGCGCCCTG
1621 AGCGTGGTGA CCGTGCCTC CAGCAGCTTG GGCACCCAGA CCTACATCTG CAACGTGAAT 1681 CACAAGCCCA GCAACACCAA GGTGGACAGA 1741 AGGGTGTCTG CTGGAAGCCA GGCTCAGCGC 1801 CCCAGTCCAG GGCAGCAAGG CAGGCCCGT TCCTGCCTGG ACCGATCCCG GCTATGCCCGC 1861 CCCACTCATG CTCAGGGAGA GGGTCTTCTG CTGCCTCGT CAGGCTCTGC CGC 1861 CCCACTCATG CTCAGGGAGA GGCTCTCTG CCTGCCTCTC CAGGCTCTGG GCAGCCAGG 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTGGG CCACCCCAAA GGCCAAACTC 1981 CAAGAGCCAT ATCCGGGAG ACCTTCTCC CTGCCTCTC CCAGCCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGCCCGGAC ACCTTCTCC CTCCCAGATT CCAGTAACTC CCACCCCAAA GGCCAAACTC 2041 TCCACTGCAG CCCAAATCTT GTGACAAAAC CCACCCTAAC CCACCCCAAA GCCCAAACTC 2161 AGCCCAGGCC TCGCCCTCCA GCTCAAGGCG GGACAGGCC CCACCCTGCC 2281 TCCTGGGGG ACCGTCAGT CTCCCAGAACC CCACCCTCAC CCCACAAACC CCACCTCAC CCCCAAAACC CCACCCTGAC 2281 TCCTGGGGG ACCGTCAGT TCCCTCTCC CCCCAAAACC CCACGAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAC TCCCTCTCTC CCCCAAAACC CAAGACACC CTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG CCCACGAGAC CCTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG CCCACCAAAACC CAAGACACAC CCCCAAAACC CCCCAAAACC CAAGACACC CTCATGAGTCA 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGGACCCC TGAGGTCAA 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGGACCCC TGAGGTCAC CCCCAAAACC CAAGACACAC CCCCAAGGGC 2461 AGCAGTACAA CAGCCAAA GGCGGTGGAG CCCCCAAAACC CCACCTGGC CCCATGAGGC 2461 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCAACAAACC CCCCAAGACC CCCCAAGGGC 2521 TGAATGGCA GGAGACACAC CCCCAAAACC CAAGACACAC CCCCAAGGGC 2641 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCCCAAAACC CCCCAAGAGC CCCCATCGAGGC 2641 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCCCAAAACC CCCCAAGAGC CCCCATCGAGGC 2641 CGGCTCGGC CACCCTTGC CCTGAAGGTC CCCCCATCCC GGGCACAT GGACCACAT GGACCACACT GGACCACAT GGACCACAT GGACCACAT GGACCACAT GGACCACACACACACACACACACACACACACACACACAC	1561	ACCAGCGGCG	TGCACACCTT	CCCGGCTGTC	CTACAGTCCT	CAGGACTCTA	CTCCCTCAGC
1681 CACAAGCCCA GCAACACCAA GGTGGACAAG AAAGTTGGTG AGAGGCAGC ACAGGGAGGG 1741 AGGGTGTCTG CTGGAAGCCA GGCTCAGCGC TCCTGCCTGG ACCCATCCCG GCTATGCAGC 1861 CCCAGTCCAG GGCACAAGG CAGGCCCCGT CTGCCCTGT ACCCGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAGGGAGA GGGTCTTCTG CTGCCCGC CAGGCTCTGG CCCACCCCAAG 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGTTGGC TCAGACCTGC 1981 CAAGAGCCAT ATCCGGGAGG ACCCTGCCCC TGACCTAAGC CCACCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGCTCGGAC ACCTTCTCC CTCCCAGATT CCAGTAACTC CCAATCTTCT 2101 CTCTGCAGAG CCCAAACTCT GTGACAAAAC CCACCGTGC CAGGTAAGCC 2221 GGGACAGGCC CCCAACACCT GCTCAAGGC GGACAGGTGC CCTAGAGTAGC 2221 GGGACAGGCC CCCAGCCGGT GCTCAACGC GGACACGTC CCACCGTGC CAGGTAAGCC 2281 TCCTGGGGG ACCGTCAGT TTCCTCTTCC CCCCAAAACC CAAGGGACAC CTCATGATCT 2341 CCCGGACCCC TGAGGTCAA TGCGTGGGG TGCACACACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCAA TGCGTGGGG GCGTGAGAG CCACGAAAAC CAAGAGACAC CTCATGATCT 2341 CCCGGACCCC TGAGGTCAA TGCGTGGGG GCGTGAGG CCACCTCAAACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCAA TGCGTGGGG GCGTGAGG CCACCAAAACC CAAGGACAAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAA GGCGTGAGG TGCATAATGC CAACAAAGC CCTGAGGTCA 2521 TGAATGGCAA GGAGCACAA GGCGTGGAGG CCCCCAAAACC CAAGACAAAG CCCGCGGAGG 2461 CGGCTCGGC CACCCTTGC CCTGAGGTCA CCAACAAAGC CCCCCAGCC CCCATCGAGA 2521 TGAATGGCAA GGAGCACAA GGTGGGACC CCCAACAAAGC CCCCCAGCC CCCATCGAGA 2521 TGAATGGCAA GGAGCACAA GGTGGGACC CCCAACAAAGC CCCCCAGCC CCCATCGAGA 2521 TGAATGCCAA GGTGGGACC CCTGAGAGAC CCCCAACAAAGC CCCCCTGGAG 2521 TGAATGGCA GGAGCACAA GGTGGGACC CCCAACAAAGC CCCCCAGCC CCCATCGAGA 2521 TGAATGGCA GGAGCACAA GGTGGGACC CCCAACAAAGC CCCCCAGCC CCCATCGAGA 2521 TGAATGGCA GGAGCACAA GGTGGGACC CCCAACAAAGC CCCCCAGCC CCCATCGAGA 2521 TGAATGGCA GGAGCACAT GCACCTCTG CCCCCAACAAAGC CTCCCGGC CCCATCGAGACC 2641 CGGCTCGGC CACCCTTGC CCTGAGAGC CCCCAACACC CCCATCGAGACC CCCAACAAAGC CCCCCTGGAGACC CCCAACACACC CCCATCGAGACC CTCCCAGCC CCCATCGAGACC CCCCAACACC CCCAACACACC CCCCAACACC CCCAACACC CCCAACACACC CCCAACACC CCCCACCCC GGACTCGC GGACTCGC GGACTCGC GGACTCGC GGACTCGC GGACTCCC GGACTCCC GGACTCCC GGACTCCC GGACTCCC CCCAACACC CCC	1621	AGCGTGGTGA	CCGTGCCCTC	CAGCAGCTTG	GGCACCCAGA	CCTACATCTG	CAACGTGAAT
1741 AGGGTGTCTG CTGGAAGCCA GGCTCAGCGC TCCTGCCTGG ACGCATCCCG GCTATGCAGC 1801 CCCAGTCCAG GGCAGCAGG CAGGCCCGT CTGCCTCTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAGGGAGA GGGTCTTCTG GCTTTTTCCC CAGGCTCTGG GCAGGCACAG 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCAC CAAAGGGGCA GGTGCTGGG CTCAGCCAG 1981 CAAGAGCCAT ATCCGGGAGG ACCTTCTCC TGACCTAAGC CCACCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGCTCGGAC ACCTTCTCTC CTCCCAGATT CCAGTAACTC CCAATCTTC 2101 CTCTGCAGAG CCCAAATCTT GTGACAAAAC TCACACATGC CCACCGTGC CAGGTAAGCC 2221 GGGACAGGCC CCAGCCGGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAC 2221 TCCTGGGGGG ACCGTCAGC CCCAAAACC TCCACCTCCAT CTCTTCCTCA GCACCTGAC 2341 CCCGGACCCC TGAGGTCACA TCCCTTTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAG CCACGAAGAC CTCATGATCT 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAG CCACGAAGAC CTCATGATCT 2401 AGTTCAACTG GTACGTGGAC CGTGTGGTG CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CACCAAAAC CAGCACGAC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCAGC CCCATCGAG 2521 TGAATGGCAA GGAGTACAAG GGTGGGACC GTGGGGCG AGGCCACAT GGACAGAGC 2521 TGAATGCCAA GGAGTACAAG GGTGGGACC CTCAACAAAGC CCTCCCAGC CCCATCGAGA 2581 AAACCATCTC CAAAGCCAAA GGTGGGACC CCCAACAAAGC CCTCCCAGC CCCATCGAGA 2641 CGGCTCGGC CACCCTCTGC CCTGAGAGTG CCCCAACAAAGC CCTCCAGCC CCCATCGAGA 2521 TGAATGGCAA GGAGTACAAG GGTGGGACC CCCAACAAAGC CCTCCCAGC CCCATCGAGA 2521 TGAATGGCAA GGAGTACAAG GGTGGGACC GTGGGGTGC AGGCCACAT GGACAGAGC 2641 CGGCTCGGC CACCCTCTGC CCTGAGAGTG CCCCAACAAAGC CCTCCCAGC CCCATCGAGA 2521 GAAGCCACG CACCCTCTG CCTGAGAGTG CCCCCATCCC GGGATGAGCT CCCTACAGGG 2641 CGGCTCGGC CACCCTCTG CCTGAGAGC CCTCCCAGC CCCATCAGGGC 2641 CGGCTCGGC CACCCTCGC CCTGAGAGAC CCTCCCAGC CCCATCAGGGC 2641 CGGCTCGGC CACCCTCGC CCTGAGAGAC CCTCCAGCC CCCATCAGGGC 2641 CGGCTCGGC CACCCTGC CCTGAGAGAC CCTCCCAGC CCCCATCGCC CCCATCAGAGC CCTCCCAGC CCCAACAACACCC CCCACCCTGC CCCAACAACACCC CCCCACCCC GGGACATCG CCCCAACACACCC CCCCACCCC GGGACACCC CCCCACCCC CCCACCCC GGGACACCC CCCCCACCC GGGACCACC GGCCCCACCC GGCACCACC CCCCCCCACCC GGGACCACC CCCCACCCC GGCACCCC CCCCACCCCCCCC	1681	CACAAGCCCA	GCAACACCAA	GGTGGACAAG	AAAGTTGGTG	AGAGGCCAGC	ACAGGGAGGG
1801 CCCAGTCCAG GGCAGCAAGG CAGGCCCGT CTGCCTCTTC ACCCGGAGGC CTCTGCCCGC 1861 CCCACTCATG CTCAGGAGA GGGTCTTCTG GCTTTTTCCC CAGGCTCTGG GCAGGCACAG 1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTGGC TCAGACCTGC 1981 CAAGAGCCAT ATCCGGGAGG ACCCTGCCCC TGACCTAAAGC CCACCCAAAA GGCCAAACTC 2041 TCCACTCCCT CAGCTCGGAC ACCTTCTCTC CTCCCAGATT CCAGTAACTC CCAATCTTCT 2101 CTCTGCAGAG CCCAAATCTT GTGACAAAAC TCACACATGC CCACCGTGCC CAGGTAAGCC 2261 AGCCCAGGCC TCGCCCTCCA GCTCAAGGCG GGACAGGTGC CCTGCATCCA 2221 GGGACAGGCC CCCAGCCGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAC 2281 TCCTGGGGG ACCGTCACA TGCCTGTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCACA TGCGTGGGG TGCGTGAG CCACCAAAACC CAAGGACACC CTCATGATCT 2401 AGTTCAACTG GTACGTGAC GGCGTGGAGG TGCACAAACC CAAGGACAAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGAC CGTGGTGAG CCACCAAAACC CAAGACAAA CCGCGGGAGG 2461 AGCAGTACAA CAGCACGAC CGTGGTGAC CGTCCTCAC CGTCCTGCAC CAGGACTGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAG 2521 TGAATGGCAA GGAGCACAAG GGTGGGACCC GTGGGGTGCA ACCCCTCAC GGGACTGGC CCCCATCGAG 2521 TGAATGGCAA GGAGCACAAA GCCTCTCCC GGGATGAGCT GACCAAGAAC 2561 CAGCCCGAA AACCACAGGT GTACACCCTG CCCCCATCCC GGGACATCG CGTGGAGGC 2641 CGGCCCGAA AACCACAGGT GTACACCCTG CCCCCATCCC GGGACATCG CGTGGAGGC 2641 CGGCCCGAA AACCACAGGT GTACACCCTG CCCCCATCCC GGGACATCG CGTGGAGGC 2641 CGGCCCGAA AACCACAGGC TTCCTCACC GGGACATCG CGTGGAGGC 2641 CGGCCCGAA AACCACCTG CCCCCATCCC GGGACATCG CGTGGAGGC 2641 CGGCCCGAA AACCACCTG CCCCCATCCC GGGACATCG CCCCTACAGGGC 2641 CGGCCCGAA AACCACCTG CCCCCATCCC GGGACATCG CCCCTACAGAGAC CCCCCATCCCGACC CCCCTACCCGCC CCCTACCCGCGC GACCACTCCC GGCACATCG CCCCCACCTCCC	1741	AGGGTGTCTG	CTGGAAGCCA	GGCTCAGCGC	TCCTGCCTGG	ACGCATCCCG	GCTATGCAGC
1861 CCCACTCATG 1921 GCTAGGTGCC 1981 CAAGAGCCAT 2041 TCCACTCCCT 2041 TCCACTCCCT 2101 CTCTGCAGAG 2101 CTCTGCAGAGAG 2101 CAGCCCGAGAGAG 2101 CAGCCCGAGAGAG 2101 CAGCCCGAGAGG 2101 CAGCCCGAGAGGG 2101 CAGCCCGAGAGGG 2101 CAGCCCGAGAGGG 2101 CAGCCCGAGAGGG 2101 CAGCCCGAGAGGG 2101 CAGCCCGAGAGGGGGAG 2101 CAGCCCGAGAGGGGGAGGGGGAGGGGGAGGGGGAGGGGGAGGGGGAGGGG	1801	CCCAGTCCAG	GGCAGCAAGG	CAGGCCCCGT	CTGCCTCTTC	ACCCGGAGGC	CTCTGCCCGC
1921 GCTAGGTGCC CCTAACCCAG GCCCTGCACA CAAAGGGGCA GGTGCTGGGC TCAGACCTGC 1981 CAAGAGCCAT ATCCGGGAGG ACCTTGCCC TGACCTAAGC CCACCCCAAA GGCCAAACTC 2041 TCCACTCCCT CAGCTCGGAC ACCTTCTCT CTCCCAGGATT CCAGTAACTC CCAATCTTCT 2101 CTCTGCAGAG CCCAAATCTT GTGACAAAAC TCACACATGC CCACCGTGCC CAGGTAAGCC 2161 AGCCCAGGCC TCGCCCTCCA GCTCAAAGCG GGACAGGTGC CCTAGAGTAG CCTGCATCCA 2221 GGGACAGGCC CCAGCGGGT GCTGAACGCG CCACCGTGCC CTGCATCCA 2281 TCCTGGGGGG ACCGTCAAGCGG TCCCCAAAACC CAAGGACAC CTCATGATCC 2341 CCCGGACCCC TGAGGTCAAC TGCGTGGTGG TGGACCTGAAC CCACGAAGAC CTCATGATCT 2341 CCCGGACCCC TGAGGTCAAC TGCGTGGTGG TGGACGTGAG CCACGAAGAC CTCATGATCA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CAGGACAAAG CCGCGGGAGG 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAG 2521 TGAATGGCAA GGAGTACAAG GTGCGGACCC GTGGGGTCG ACGCCCAGACAC CAAGCCACAT GGACAGAGC 2521 TGAATGGCAA GGTGGGACCC GTGGGGTCG ACGCCCACACACACC CCCCATCGAGA 2521 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGACC CCCCATCGAGAC 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGACC CCCCATCAGGC 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGACC CCTCACAGACC 2701 CAGCCCCGAG GACCACAGG TTACACCCTG CCCCCATCCC GGGATGACC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGGT GTACACCCTG CCCCCATCCC GGGATGACC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGGG GTACACCCTG CCCCCATCCC GGGATGACC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGG GTACACCCTG CCCCCATCCC GGGATGACC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGG GTACACCCTG CCCCCATCCC GGGACTGCC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGG GTACACCCTG CCCCCATCCC GGGACTGCC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGC CTCCCGACCC CCCCCATCCC GGGACTGCC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGC CTCCCACCC CCCCCATCCC GGGACTGCC CGTGGAGTGG 2701 CAGCCCCGAG GACCACGC CTCCCACCC CCCCACCCC CCCCACCCCCC	1861	CCCACTCATG	CTCAGGGAGA	GGGTCTTCTG	GCTTTTTCCC	CAGGCTCTGG	GCAGGCACAG
1981 CAAGAGCCAT 2041 TCCACTCCT 2041 TCCACTCCT CAGCTCGGAC ACCTTCTCT CTCTGCAGAG CCCAAATCTT GTGACAAAAC TCACACATGC CCACCCCAAA CCAATCTTCT CTCTGCAGAG CCCAAATCTT GTGACAAAAC TCACACATGC CCACCGTGCC CAGGTAACTC CCAGTTAACC CCAATCTTCT CCAGTTAACC CCAACCTCCA CCAATCTTCT CCAGTTAACC CCAACCTCCA CCACCGTGCC CAGGTAACCC CCAGCTGACC CCAGCCGGGT GCTCAAGGCG GGACAGGTC CCACCTCCAT CTCTTCCTCA GCACCTCAT CCTCTTCCA CCACCTCCAT CCTCTTCCTCA CCACCTCCAT CCTCTTCCTCA CCACCTCCAT CCTCTTCCTCA CCACCTCCAT CCTCTTCCTCA CCACCTCCAT CCTCTTCCTCA CCACCTCCAC CCTCTGAACC CCACCTCCAC CCACCTCAC CCACCACAAAC CCCCCAGCC CCACCTCGC CCACCACAAAC CCCCCTCCCAC CCCATCCAGC CCCACCACAAAC CCCCTCCCCC CCCACCC CCCACCCC CCCACCCC CCCACCCC CCCACCCC CCCACCCC CCCACCCC CCCACCC CCCACCCC CCCCACCC CCCACCCC CCCCACCC CCCCACCC CCCCACCC CCCCACCC CCCCCC	1921	GCTAGGTGCC	CCTAACCCAG	GCCCTGCACA	CAAAGGGGCA	GGTGCTGGGC	TCAGACCTGC
2041TCCACTCCCTCAGCTCGGACACCTTCTCTCTCCCAGATTCCAGTAACTCCCAATCTTCT2101CTCTGCAGAGCCCAAATCTTGTGACAAAACTCACACATGCCCACCGTGCCCAGGTAAGCC2161AGCCCAGGCCTCGCCCTCCAGCTCAAGGCGGGACAGGTGCCCTAGAGTAGCCTGCATCCA2221GGGACAGGCCCCAGCCGGGTGCTGACACGTCCACCTCCATCTCTTCCTCAGCACCTGAAC2341CCCGGACCCCTGAGGTCACATGCGTGGTGGTGGACGTGAGCCACGAAGACCCTGAGGTCA2401AGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG2461AGCAGTACAACAGCACGTACCGTGTGGTCACGTCCTCACCGTCCTGCACCAGGACTGGC2521TGAATGGCAAGGAGTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAGCCCCCATCGAGA2581AAACCATCTCCAAAGCCAAAGGTGGGACCGTGGGGTGCGAGGGCCACATGGACAGAGGC2641CGGCTCGGCCCACCCTCTGCCCTGAGAGTGCACCCTGTGCCCTGACAGGCCTCCCATCCCGGGACACATGGACAAGAGC2701CAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGCCCAAGAGCCCTGAGAGGC2761CAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCCAGCACATCGCCGTGGAGTGG2821GAGAGCAATGGGCAGCCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGAC2881GGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAAC2941GTCTTCTCATGCTCCGTGATGCATGAGACCACTA							
2101 CTCTGCAGAG CCCAAATCTT GTGACAAAAC TCACACATGC CCACCGTGCC CAGGTAAGCC 2161 AGCCCAGGCC TCGCCCTCCA GCTCAAGGCG GGACAGGTGC CCTAGAGTAG CCTGCATCCA 2221 GGGACAGGCC CCAGCCGGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAAC 2281 TCCTGGGGGG ACCGTCAGTC TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCACA TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAG 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCC GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2161 AGCCCAGGCC TCGCCCTCA GCTCAAGGCG GGACAGGTGC CCTAGAGTAG CCTGCATCCA 2221 GGGACAGGCC CCAGCCGGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAAC 2281 TCCTGGGGGG ACCGTCAGTC TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCACA TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAG 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCCTG GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGCC CTGCACAACC ACTACACGCA GAAGAGCCTC							
2221 GGGACAGGCC CCAGCCGGGT GCTGACACGT CCACCTCCAT CTCTTCCTCA GCACCTGAAC 2281 TCCTGGGGGG ACCGTCAGTC TTCCTCTTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCACA TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAG 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC	2161	AGCCCAGGCC	TCGCCCTCCA	CCTCAAGGCG	GGACACGTGC	CCTACACTAC	CCTCCATCCA
2281 TCCTGGGGGG ACCGTCAGTC TTCCTCTCC CCCCAAAACC CAAGGACACC CTCATGATCT 2341 CCCGGACCCC TGAGGTCACA TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2341 CCCGGACCCC TGAGGTCACA TGCGTGGTGG TGGACGTGAG CCACGAAGAC CCTGAGGTCA 2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2401 AGTTCAACTG GTACGTGGAC GGCGTGGAGG TGCATAATGC CAAGACAAAG CCGCGGGAGG 2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2461 AGCAGTACAA CAGCACGTAC CGTGTGGTCA GCGTCCTCAC CGTCCTGCAC CAGGACTGGC 2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2521 TGAATGGCAA GGAGTACAAG TGCAAGGTCT CCAACAAAGC CCTCCCAGCC CCCATCGAGA 2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2581 AAACCATCTC CAAAGCCAAA GGTGGGACCC GTGGGGTGCG AGGGCCACAT GGACAGAGGC 2641 CGGCTCGGC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC	2401	MCLAGTACAA	CAGCACGTAC	CGTGTGGTCA	GCGTCCTCAC	CGTCCTGCAC	CAGGACTGGC
2641 CGGCTCGGCC CACCCTCTGC CCTGAGAGTG ACCGCTGTAC CAACCTCTGT CCCTACAGGG 2701 CAGCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC	2221	IGAATGGCAA	GGAGTACAAG	TGCAAGGTCT	CCAACAAAGC	CCTCCCAGCC	CCCATCGAGA
2701 CAGCCCGAG AACCACAGGT GTACACCCTG CCCCCATCCC GGGATGAGCT GACCAAGAAC 2761 CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2761 CAGGTCAGCC TGACCTGCCT GGTCAAAGGC TTCTATCCCA GCGACATCGC CGTGGAGTGG 2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2821 GAGAGCAATG GGCAGCCGGA GAACAACTAC AAGACCACGC CTCCCGTGCT GGACTCCGAC 2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC	2701	CAGCCCCGAG	AACCACAGGT	GTACACCCTG	CCCCCATCCC	GGGATGAGCT	GACCAAGAAC
2881 GGCTCCTTCT TCCTCTACAG CAAGCTCACC GTGGACAAGA GCAGGTGGCA GCAGGGGAAC 2941 GTCTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
2941 GTCTTCTCAT GCTCCGTGAT GCATGAGGCT CTGCACAACC ACTACACGCA GAAGAGCCTC							
3001 TCCCTGTCTC CGGGTAAATG AGTGCGACGG CCGGCAAGCC CCCGCTCCCC GGGCTCTCGC							
	3001	TCCCTGTCTC	CGGGTAAATG	AGTGCGACGG	CCGGCAAGCC	CCCGCTCCCC	GGGCTCTCGC

FIG. 13A

3061	GGTCGCACGA	GGATGCTTGG	CACGTACCCC	CTGTACATAC	TTCCCGGGCG	CCCAGCATGG
3121	AAATAAAGCA	CCCAGCGCTG	CCCTGGGCCC	CTGCGAGACT	GTGATGGTTC	TTTCCACGGG
3181	TCAGGCCGAG	TCTGAGGCCT	GAGTGGCATG	AGGGAGGCAG	AGCGGGTCCC	ACTGTCCCCA
	CACTGGCCCA	GGCTGTGCAG	GTGTGCCTGG			
3301	GCCCTCGGCA	GGGTGGGGGA	TTTGCCAGCG	TGGCCCTCCC	TCCAGCAGCA	CCTGCCCTGG
3361	GCTGGGCCAC	GGGAAGCCCT	AGGAGCCCCT	GGGGACAGAC	ACACAGCCCC	TGCCTCTGTA
3421	GGAGACTGTC	CTGTTCTGTG	AGCGCCCCTG	TCCTCCCGAC	CTCCATGCCC	ACTCGGGGGC
3481	ATGCCTAGTC	CATGTGCGTA	GGGACAGGCC	CTCCCTCACC	CATCTACCCC	CACGGCACTA
3541	ACCCCTGGCT	GCCCTGCCCA	GCCTCGCACC	CGCATGGGGA	CACAACCGAC	TCCGGGGACA
3601	TGCACTCTCG	GGCCCTGTGG	AGGGACTGGT	GCAGATGCCC	ACACACACAC	TCAGCCCAGA
3661	CCCGTTCAAC	AAACCCCGCA	CTGAGGTTGG	CCGGCCACAC	GGCCACCACA	CACACACGTG
3721	CACGCCTCAC	ACACGGAGCC	TCACCCGGGC	GAACTGCACA	GCACCCAGAC	CAGAGCAAGG
3781	TCCTCGCACA	CGTGAACACT	CCTCGGACAC	AGGCCCCCAC	GAGCCCCACG	CGGCACCTCA
3841	AGGCCCACGA	GCCTCTCGGC	AGCTTCTCCA	CATGCTGACC	TGCTCAGACA	AACCCAGCCC
3901	TCCTCTCACA	AGGGTGCCCC	TGCAGCCGCC	ACACACACAC	AGGGGATCAC	ACACCACGTC
3961	ACGTCCCTGG	CCCTGGCCCA	CTTCCCAGTG	CCGCCCTTCC	CTGCAGGACG	
4021	GACTGTGCCT	TCTAGTTGCC	AGCCATCTGT	TGTTTGCCCC	TCCCCCGTGC	
4081	CCTGGAAGGT	GCCACTCCCA			GAGGAAATTG	
4141		TGTCATTCTA		TGGGGTGGGG	CAGGACAGCA	AGGGGGAGGA
4201	TTGGGAAGAC	AATAGCAGGC	ATGCTGGGGA		TCTATGGCTT	
4261		TGGGGCTCTA			TGTAGCGGCG	
4321	GGCGGGTGTG	GTGGTTACGC	GCAGCGTGAC	CGCTACACTT		TAGCGCCCGC
4381			CCTTTCTCGC		GGGCCTCTCA	
4441	AAAAAGCATG	CATCTCAATT			CCCCTAACTC	
4501			CCGCCCATTC	TCCGCCCCAT	GGCTGACTAA	
4561	TTATGCAGAG	GCCGAGGCCG			CAGAAGTAGT	
4621		CTAGGCTTTT			AGGGCTGCGA	
4681		CAATCCTAGC		GTAGGATTTT	ATCCCCGCTG	
4741	TCGACCATTG	AACTGCATCG	TCGCCGTGTC		GGGATTGGCA	
4801	CCTACCCTGG	CCTCCGCTCA	GGAACGAGTT	CAAGTACTTC	CAAAGAATGA	
4861		GGTAAACAGA				
4921	TGAGAAGAAT	CGACCTTTAA	AGGACAGAAT		CTCAGTAGAG	
4981		GGAGCTCATT			GATGCCTTAA	
5041		TTGGCAAGTA				
5101	CCAGGAAGCC	ATGAATCAAC	CAGGCCACCT	TACA CTCTTTT	GTGACAAGGA	
		GACACGTTTT				
		GTCCTCTCTG				TTCTCCCAGA
5281	CTACCACAAC	AAAGACTAAC	AGGICCAGGA	MMMC3 3 CMMC		
		ATAAGACCAT			TCTGCTCCCC	TCCTAAAGCT
5401	TIGCATITIE	GTGTGACATA	AMMCCACAAA	CIGGCITTAG	ATCTCTTTGT	GAAGGAACCT
5461						CTCTAAGGTA
5521		TTTTAAGTGT				
	A A COMOMOMO	CCTATGGAAC	TGATGAATGG	GAGCAGTGGT	GGAATGCCTT	TAATGAGGAA
5561	CARROTTITI	GCTCAGAAGA	AATGCCATCT	AGTGATGATG	AGGCTACTGC	TGACTCTCAA
5701	CATTCTACTC	CTCCAAAAA	GAAGAGAAAG	GTAGAAGACC	CCAAGGACTT	TCCTTCAGAA
5701	TIGCIAAGTT	TTTTGAGTCA	TGCTGTGTTT	AGTAATAGAA	CTCTTGCTTG	CTTTGCTATT
2/01	ACACCACAA	AGGAAAAAGC	TGCACTGCTA	TACAAGAAAA	TTATGGAAAA	ATATTCTGTA
2827	ACCITITATAA	GTAGGCATAA	CAGTTATAAT	CATAACATAC	TGTTTTTCT	TACTCCACAC
2881	AGGCATAGAG	TGTCTGCTAT	TAATAACTAT	GCTCAAAAAT	TGTGTACCTT	TAGCTTTTTA
3941 6001	ATTTGTAAAG	GGGTTAATAA	GGAATATTTG	ATGTATAGTG	CCTTGACTAG	AGATCATAAT
6001	CAGCCATACC	ACATTTGTAG	AGGTTTTACT	TGCTTTAAAA	AACCTCCCAC	ACCTCCCCCT
0061	GAACCTGAAA	CATAAAATGA	ATGCAATTGT	TGTTGTTAAC	TTGTTTATTG	CAGCTTATAA

FIG. 13B

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6121 TGGTTACAAA TAAAGCAATA GCATCACAAA TTTCACAAAT AAAGCATTTT TTTCACTGCA
6181 TTCTAGTTGT GGTTTGTCCA AACTCATCAA TGTATCTTAT CATGTCTGGA TCGGCTGGAT 6241 GATCCTCCAG CGCGGGGATC TCATGCTGGA GTTCTTCGCC CACCCCAACT TGTTTATTGC 6301 AGCTTATAAT GGTTACAAAT AAAGCAATAG CATCACAAAT TTCACAAATA AAGCATTTTT 6361 TTCACTGCAT TCTAGTTGTG GTTTGTCCAA ACTCATCAAT GTATCTTATC ATGTCTGTAT
6421 ACCGTCGACC TCTAGCTAGA GCTTGGCGTA ATCATGGTCA TAGCTGTTTC CTGTGTGAAA
6481 TTGTTATCCG CTCACAATTC CACACAACAT ACGAGCCGGA AGCATAAAGT GTAAAGCCTG
6541 GGGTGCCTAA TGAGTGAGCT AACTCACATT AATTGCGTTG CGCTCACTGC CCGCTTTCCA
6601 GTCGGGAAAC CTGTCGTGCC AGCTGCATTA ATGAATCGGC CAACGCGCGG GGAGAGGCGG
6661 TTTGCGTATT GGGCGCTCTT CCGCTTCCTC GCTCACTGAC TCGCTGCGCT CGGTCGTTCG
6721 GCTGCGGCGA GCGGTATCAG CTCACTCAAA GGCGGTAATA CGGTTATCCA CAGAATCAGG
6781 GGATAACGCA GGAAAGAACA TGTGAGCAAA AGGCCAGCAA AAGGCCAGGA ACCGTAAAAA
6841 GGCCGCGTTG CTGGCGTTTT TCCATAGGCT CCGCCCCCCT GACGAGCATC ACAAAAATCG
6901 ACGCTCAAGT CAGAGGTGGC GAAACCCGAC AGGACTATAA AGATACCAGG CGTTTCCCCC
6961 TGGAAGCTCC CTCGTGCGCT CTCCTGTTCC GACCCTGCCG CTTACCGGAT ACCTGTCCGC
7021 CTTTCTCCCT TCGGGAAGCG TGGCGCTTTC TCAATGCTCA CGCTGTAGGT ATCTCAGTTC
7081 GGTGTAGGTC GTTCGCTCCA AGCTGGGCTG TGTGCACGAA CCCCCCGTTC AGCCCGACCG
7141 CTGCGCCTTA TCCGGTAACT ATCGTCTTGA GTCCAACCCG GTAAGACACG ACTTATCGCC
7201 ACTGGCAGCA GCCACTGGTA ACAGGATTAG CAGAGCAGG TATGTAGGCG GTGCTACAGA
7261 GTTCTTGAAG TGGTGGCCTA ACTACGGCTA CACTAGAAGG ACAGTATTTG GTATCTGCGC
7321 TCTGCTGAAG CCAGTTACCT TCGGAAAAAG AGTTGGTAGC TCTTGATCCG GCAAACAAAC
7381 CACCGCTGGT AGCGGTGGTT TTTTTGTTTG CAAGCAGCAG ATTACGCGCA GAAAAAAAAGG
7441 ATCTCAAGAA GATCCTTTGA TCTTTTCTAC GGGGTCTGAC GCTCAGTGGA ACGAAAAACTC
7501 ACGTTAAAGG ATTTTGGTCA TGAGATTATC AAAAAGGTC TTCACCTAGA TCCTTTTTAAA
7561 TTAAAAATGA AGTTTTAAAT CAATCTAAAG TATATATGAG TAAACTTGGT CTGACAGTTA
7621 CCAATGCTTA ATCAGTGAGG CACCTATCTC AGCGATCTGT CTATTTCGTT CATCCATAGT
7681 TGCCTGACTC CCCGTCGTGT AGATAACTAC GATACGGGAG GGCTTACCAT CTGGCCCCAG
7741 TGCTGCAATG ATACCGCGAG ACCCACGCTC ACCGGCTCCA GATTTATCAG CAATAAACCA
7801 GCCAGCCGGA AGGGCCGAGC GCAGAAGTGG TCCTGCAACT TTATCCGCCT CCATCCAGTC
7861 TATTAATTGT TGCCGGGAAG CTAGAGTAAG TAGTTCGCCA GTTAATAGTT TGCGCAACGT
7921 TGTTGCCATT GCTACAGGCA TCGTGGTGTC ACGCTCGTCG TTTGGTATGG CTTCATTCAG
7981 CTCCGGTTCC CAACGATCAA GGCGAGTTAC ATGATCCCCC ATGTTGTGCA AAAAAGCGGT
8041 TAGCTCCTTC GGTCCTCCGA TCGTTGTCAG AAGTAAGTTG GCCGCAGTGT TATCACTCAT
8101 GGTTATGGCA GCACTGCATA ATTCTCTTAC TGTCATGCCA TCCGTAAGAT GCTTTTCTGT
8161 GACTGGTGAG TACTCAACCA AGTCATTCTG AGAATAGTGT ATGCGGCGAC CGAGTTGCTC
8221 TTGCCCGGCG TCAATACGGG ATAATACCGC GCCACATAGC AGAACTTTAA AAGTGCTCAT
8281 CATTGGAAAA CGTTCTTCGG GGCGAAAACT CTCAAGGATC TTACCGCTGT TGAGATCCAG
8341 TTCGATGTAA CCCACTCGTG CACCCAACTG ATCTTCAGCA TCTTTTACTT TCACCAGCGT
8401 TTCTGGGTGA GCAAAAACAG GAAGGCAAAA TGCCGCAAAA AAGGGAATAA GGGCGACACG
8461 GAAATGTTGA ATACTCATAC TCTTCCTTTT TCAATATTAT TGAAGCATTT ATCAGGGTTA
8521 TTGTCTCATG AGCGGATACA TATTTGAATG TATTTAGAAA AATAAACAAA TAGGGGTTCC
8581 GCGCACATTT CCCCGAAAAG TGCCACCTGA CGTC
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FIG. 13C

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1	GACGGATCGG	GAGATCTGCT	AGCCCGGGTG	ACCTGAGGCG	CGCCGGCTTC	GAATAGCCAG
61	AGTAACCTTT	TTTTTTAATT	TTATTTTATT	TTATTTTGA	GATGGAGTTT	GGCGCCGATC
121	TCCCGATCCC	CTATGGTCGA	CTCTCAGTAC	AATCTGCTCT	GATGCCGCAT	AGTTAAGCCA
181	GTATCTGCTC	CCTGCTTGTG	TGTTGGAGGT	CGCTGAGTAG	TGCGCGAGCA	AAATTTAAGC
241	TACAACAAGG	CAAGGCTTGA	CCGACAATTG	CATGAAGAAT	CTGCTTAGGG	TTAGGCGTTT
301	TGCGCTGCTT	CGCGATGTAC	GGGCCAGATA	TACGCGTTGA	CATTGATTAT	TGACTAGTTA
361	TTAATAGTAA	TCAATTACGG	GGTCATTAGT	TCATAGCCCA	TATATGGAGT	TCCGCGTTAC
421	ATAACTTACG	GTAAATGGCC	CGCCTGGCTG	ACCGCCCAAC	GACCCCCGCC	CATTGACGTC
481	AATAATGACG	TATGTTCCCA	TAGTAACGCC	AATAGGGACT	TTCCATTGAC	GTCAATGGGT
541	GGACTATTTA	CGGTAAACTG	CCCACTTGGC	AGTACATCAA	GTGTATCATA	TGCCAAGTAC
601	GCCCCTATT	GACGTCAATG	ACGGTAAATG	GCCCGCCTGG	CATTATGCCC	AGTACATGAC
661	CTTATGGGAC	TTTCCTACTT	GGCAGTACAT	CTACGTATTA	GTCATCGCTA	TTACCATGGT
721	GATGCGGTTT	TGGCAGTACA	TCAATGGGCG	TGGATAGCGG	TTTGACTCAC	GGGGATTTCC
781	AAGTCTCCAC	CCCATTGACG	TCAATGGGAG	TTTGTTTTGG	CACCAAAATC	AACGGGACTT
841	TCCAAAATGT	CGTAACAACT	CCGCCCCATT	GACGCAAATG	GGCGGTAGGC	GTGTACGGTG
901	GGAGGTCTAT	ATAAGCAGAG	CTCTCTGGCT	AACTAGAGAA	CCCACTGCTT	ACTGGCTTAT
961	CGAAATTAAT	ACGACTCACT	ATAGGGAGAC	CCAAGCTTGG	TACCATGGAA	GCCCCAGCTC
1021	AGCTTCTCTT	CCTCCTGCTA	CTCTGGCTCC	CAGATACCAC	CGGAGACATT	GTTCTGACTC
1081	AGTCTCCAGC	CACCCTGTCT	GTGACTCCAG	GAGATAGAGT	CTCTCTTTCC	TGCAGGGCCA
1141	GCCAGAGTAT	TAGCGACTAC	TTACACTGGT	ATCAACAAAA	ATCACATGAG	TCTCCAAGGC
1201	TTCTCATCAA	ATATGCTTCC	CATTCCATCT	CTGGGATCCC	CTCCAGGTTC	AGTGGCAGTG
1261	GATCAGGGTC	AGATTTCACT	CTCAGTATCA	ACAGTGTGGA	ACCTGAAGAT	GTTGGAATTT
1321	<u>ATTACTGTCA</u>	ACATGGTCAC	AGCTTTCCGT	GGACGTTCGG	TGGAGGCACC	AAGCTGGAAA
1381	TCAAACGTAA	GTCTCGAGTC	TCTAGATAAC	CGGTCAATCG	GTCAATCGAT	TGGAATTCTA
1441	AACTCTGAGG	GGGTCGGATG	ACGTGGCCAT	TCTTTGCCTA	AAGCATTGAG	TTTACTGCAA
1501	GGTCAGAAAA	GCATGCAAAG	CCCTCAGAAT	GGCTGCAAAG	AGCTCCAACA	AAACAATTTA
1561	GAACTTTATT	AAGGAATAGG	GGGAAGCTAG	GAAGAAACTC	AAAACATCAA	GATTTTAAAT
1621	ACGCTTCTTG	GTCTCCTTGC	TATAATTATC	TGGGATAAGC	ATGCTGTTTT	CTGTCTGTCC
1681	CTAACATGCC	CTTATCCGCA	AACAACACAC	CCAAGGGCAG	AACTTTGTTA	CTTAAACACC
1741	ATCCTGTTTG	CTTCTTTCCT	CAGGAACTGT	GGCTGCACCA	TCTGTCTTCA	TCTTCCCGCC
1801	ATCTGATGAG	CAGTTGAAAT	CTGGAACTGC	CTCTGTTGTG	TGCCTGCTGA	ATAACTTCTA
1861	TCCCAGAGAG	GCCAAAGTAC	AGTGGAAGGT	GGATAACGCC	CTCCAATCGG	GTAACTCCCA
1921	GGAGAGTGTC	ACAGAGCAGG	ACAGCAAGGA	CAGCACCTAC	AGCCTCAGCA	GCACCCTGAC
1981	GCTGAGCAAA	GCAGACTACG	AGAAACACAA	AGTCTACGCC	TGCGAAGTCA	CCCATCAGGG
2041	CCTGAGCTCG	CCCGTCACAA	AGAGCTTCAA	CAGGGGAGAG	TGTTAGAGGG	AGAAGTGCCC
2101	CCACCTGCTC					
2161	CACAGGGGAC	CTACCCCTAT	TGCGGTCCTC	CAGCTCATCT	TTCACCTCAC	CCCCCTCCTC
2221	CTCCTTGGCT	TTAATTATGC	TAATGTTGGA	GGAGAATGAA	TAAATAAAGT	GAATCTTTGC
	ACCTGTGGTT					
	AATTTCTCTT					
2401	ATCATCCTTC	ATTCTATTTT	ACCCTATCAT	CCTCTGCAAG	ACAGTCCTCC	CTCAAACCCA
2461	CAAGCCTTCT	GTCCTCACAG	TCCCCTGGGC	CATGGTAGGA	GAGACTTGCT	TCCTTGTTT
2521	CCCCTCCTCA	GCAAGCCCTC	ATAGTCCTTT	TTAAGGGTGA	CAGGTCTTAC	AGTCATATAT
2581	CCTTTGATTC	AATTCCCTGA	GAATCAACCA	AAGCAAATTT	TTCAAAAGAA	GAAACCTGCT
	ATAAAGAGAA					
	TAAACAAACA					
	TGCCTTATTT					
2821	AGTACTTTCC	ACAACCTAAT	TTAATCCACA	CTATACTCTC	ΔζΆΤΤΑΝΑΝ	CATTCATTAA
2881	AATGTTGCAA	AGGTTCTATA	AAGCTGAGAG	ACAAATATAT	ጥርጥልጥል ልርጥር	AGCAATCCCA
2941	CTTCTAGATG	ACTGAGTGTC	CCCACCCACC		CCAACAATCT	TCAAAGCAGC
3001	TTTATTTACA	AAAGCCAAAA	ATTGGAAATA	CCCCSTOTA	CCYYCYYLAI	A A TICA COTTAIN
			Gonnain	CCCCGWIIGI	CCUNCUMING	WATCHGITUT

FIG. 14A

3061	TAAACTGTGG	TATGTTTATA	CATTAGAATA	CCCAATGAGG	AGAATTAACA	AGCTACAACT
3121	ATACCTACTC	ACACAGATGA	ATCTCATAAA	AATAATGTTA	CATAAGAGAA	ACTCAATGCA
3181	AAAGATATGT	TCTGTATGTT	TTCATCCATA	TAAAGTTCAA	AACCAGGTAA	AAATAAAGTT
3241	AGAAATTTGG	ATGGAAATTA	CTCTTAGCTG	GGGGTGGGCG	AGTTAGTGCC	TGGGAGAAGA
3301	CAAGAAGGGG	CTTCTGGGGT	CTTGGTAATG	TTCTGTTCCT	CGTGTGGGGT	TGTGCAGTTA
3361	TGATCTGTGC	ACTGTTCTGT	ATACACATTA	TGCTTCAAAA	TAACTTCACA	TAAAGAACAT
3421	CTTATACCCA	GTTAATAGAT	AGAAGAGGAA	TAAGTAATAG	GTCAAGACCA	ACGCAGCTGG
3481	TAAGTGGGGG	CCTGGGATCA	AATAGCTACC	TGCCTAATCC	TGCCCWCTTG	AGCCCTGAAT
3541	GAGTCTGCCT	TCCAGGGCTC	AAGGTGCTCA	ACAAAACAAC	AGGCCTGCTA	TTTTCCTGGC
3601	ATCTGTGCCC	TGTTTGGCTA	GCTAGGAGCA	CACATACATA	GAAATTAAAT	GAAACAGACC
3661	TTCAGCAAGG	GGACAGAGGA	CAGAATTAAC	CTTGCCCAGA	CACTGGAAAC	CCATGTATGA
3721	ACACTCACAT	GTTTGGGAAG	GGGGAAGGGC	ACATGTAAAT	GAGGACTCTT	CCTCATTCTA
3781	TGGGGCACTC	TGGCCCTGCC	CCTCTCAGCT	ACTCATCCAT	CCAACACACC	TTTCTAAGTA
3841	CCTCTCTCTG	CCTACACTCT	GAAGGGGTTC	AGGAGTAACT	AACACAGCAT	CCCTTCCCTC
3901	AAATGACTGA	CAATCCCTTT	GTCCTGCTTT	GTTTTTCTTT	CCAGTCAGTA	CTGGGAAAGT
3961	GGGGAAGGAC	AGTCATGGAG	AAACTACATA	AGGAAGCACC	TTGCCCTTCT	GCCTCTTGAG
4021	AATGTTGATG	AGTATCAAAT	CTTTCAAACT	TTGGAGGTTT	GAGTAGGGGT	GAGACTCAGT
4081	AATGTCCCTT	CCAATGACAT	GAACTTGCTC	ACTCATCCCT	GGGGGCCAAA	TTGAACAATC
4141	AAAGGCAGGC	ATAATCCAGT	TATGAATTCT	TGCGGCCGCT	TECTACCTTC	ACCTCTTGGA
4201	TCCAACCGCG	GAAGGGCCCT	ATTCTATAGT	GTCACCTAAA	TGCTAGAGCT	CGCTGATCAG
4261	CCTCGACTGT	GCCTTCTAGT	TGCCAGCCAT	CTGTTGTTTG	CCCCTCCCCC	GTGCCTTCCT
4321	TGACCCTGGA	AGGTGCCACT	CCCACTGTCC	TTTCCTAATA	AAATGAGGAA	ATTGCATCGC
4381	ATTGTCTGAG	TAGGTGTCAT	TCTATTCTGG	GGGGTGGGGT	GGGGCAGGAC	AGCAAGGGGG
4441	AGGATTGGGA	AGACAATAGC	AGGCATGCTG	GGGATGCGGT	GGGCTCTATG	GCTTCTGAGG
				ATCCCCACGC		
				TGACCGCTAC		
4621	CCGCTCCTTT	CGCTTTCTTC	CCTTCCTTTC	TCGCCACGTT	CGCCGGGCCT	CTCAAAAAAG
				CAACCATAGT		
				ATTCTCCGCC		
4801				CCTCTGAGCT		
				AGCTTGGACA		
				GCTGGTAGGA		
				TGTCCCAAAA		
				AGTTCAAGTA		
				TGATTATGGG		
				GAATTAATAT		
				CCAAAAGTTT		
				ACATGGTTTG		
				ACCITAGACT		
				AAATTGATTT		
				AGGAGGAAAA		
5521	AACTOTACCA	CANCANACAC	TARCAGGICC	ATGCTTTCAA	CERCALCARG	CCCCTCCTA
				TTTGCTGGCT		
				CAAACTACCT		
				TGTTAAACTA		
				ATGGGAGCAG		
				ATCTAGTGAT		
				AAAGGTAGAA GTTTAGTAAT		
				GCTATACAAG TAATCATAAC		
9091	TGTAACCTTT	ATAAGTAGGC	ATAACAGTTA	TAATCATAAC	ATACTGTTTT	TICTIACTCC

FIG. 14B

6181 TITANTITES ANAGGGGTTA ATAGANTA CTATECTERA AGTECTTEA CETTAGETTA CASTAGEATA ANAGGGTTA ATAGANTA TITEATETTA AGTECTTEA CTAGAGATCA CASALATACACA TACCACATT GIAGAGGTTA TACTAGETT AAACTACTA AAAAAACCT CACACACCTCA CASALATACACA ATAAACACT CAAAATTCACA AAAAAACCT CACACCTCA CAAAATTCACA ATAAAAGCA ATTCATCATT TACTAGTTT TACTAGTTT TACATTCACACACACCTCA CAAAATTCACA AAAAAAACCT CAAAATTCACA AAAAAAACCA CAAAATTCACA AAAAAAACCA CAAAATTCACA AAAAAAACCA CAAAATTCACA CAAAATTCACA CAAAATTCACA CAAAATTCACA CAAAATTCACA CAAAATTCACA CAAAATTCACACA CAAAATTCACAC CAAAATTCACAC CAAAATTCACAC CAAAATTCACAC CAAAATTCACAC CAAAATTCACAC CAAAATTCACAC CAAAATTCACACA CAAAATTCACACA CAAAATACACCC CAACACTCAGT TACCACCAC AATAAAACCA CAAAATTCACACA CAAAATTCACACA CAAAATTCACACA CAATAAAACCA CAAAATTCACACA CAAAATTCACACA CAATAAAACCAT TACCACCACA CAATAAATA							
6121 TATATTET ANAGGGETTA ATANGGANTA TTUCATGETTA ANAAACCTC CACACCTCC 6201 CCCTGAACCT GAACACTATA ATGAGGTTT TACTTGCTTT TAAAAACCTC CCACCTCC 6361 ATANTAGGTTA CAAATTAAAC ATGATGCAA TTGTTGTTGTT TAACTTGTTT AAAAACCTC CCACCTCC 6361 ATANTAGGTTA CAAATTAAAC ATGATGCATCA CAAATTTCAC AAATTAAACCA 6421 TGCATCTCTAG TTGTGGTTTT TCCAAACTCA TCAATGTTC CGCCCACCCC AACTTGTTTCAC 6481 GGATGATCCT CCAGGCGGG GATCTCATG TGGAGTTCT CGCCCACCCC AACTTGTTTA 6601 TTTTTCACT GCATTCTAGT TGTGGTTTG CCAAACTCAT CAAATTACAC AAATTTCACA AAATTAACCAT 6601 TATTTCACT GACTTCTAGT TGTGGTTTGT CCAAACTCAT CAAATTACACT AAAATTACACA AAATTACACT 6601 TATTACCACC GACCTCTAGC TAGGGCTTGG CGTAACTCAA CAAATTACCAC AAATTACCAC 6601 TATTACCACC GACCTCTAGC TAGGGCTTGG CGTAACTCAA CAAATTACCAC 6781 CCCTGGGGTGC CTAAATCACA ATTCACCACA ACTAACTCAC 6781 CCCTGGGTGC CTAATCAGC ACTAACTCAA CATTAATTGAC GTTGCCCCCTT 6721 GAAATTGTTA TCCGCTCACA ATTCACCACA ACTAACTCAC 6781 CCCTGGGTGC CTAATCAGC CAAAACCCGTC CTCCCCCCTT 6841 TCCGGCTCCG GCGAGCGGTA TCACCCACA AACTACCACA CATTAATTACAC 6781 CCCCGGCTGC GCGAGCGGTA TCACCCAC CAAAAGGCCA TACCCCCC TGACCCCC CTCCCCCCTT 6841 TCCGGCTCCG GCGAGCACC AACACCCCCC TGACCCCCC AACACCCCCC AAACCCGCTC 6901 GCGCTTTCC GCAACCACA AACATCACAC CCCCGTACCC TGACCCCCC 6901 GCGCTTTCC GCACCACAAAAAACACTGTCA CATTAATTAAT 7021 CAGGGGATAA CGCAGCAAAA AACATTCAGC CAAAAGGCCA TATAACACATA 7021 CACCCTTCCG GTTCCTTCTTTCCATA GGCTCCCCCCT TCCCACCACAAAAA 7141 ATCCACGCTC CCCTTCGGGA ACCCTCCTT TCCGACCCAC AAGACCCCC GTCACACAAAA 7141 CCCCCTCCTC GAAGCCACT TCCAACCTG TTCCAACCACCCC GTTAACCAGAT TACCACCACA AACACACCAC AACACACACAAAAAACACACCAC	6121	ACACAGGCAT	AGAGTGTCTG	CTATTAATAA	CTATGCTCAA	AAATTGTGTA	CCTTTAGCTT
6301 CCCTGAACCT GAACATATA 6301 CCCCTGAACCT GAACATATA 6301 CCCCTGAACCT 6301 CTCCAACCTC 6301 CTCCAACCTC 6421 TGCATCTAG 6421 TGCATCTAG 6431 GGATGATCCT 6431 GGATGATCCT 6441 TGCAGCTTA 6541 TTGCAGCTT 6541 TTGCAGCTT 6541 TTGCAGCTTA 6541 TTGCAGCTTA 6541 TTGCAGCTTA 6541 TTGCAGCTTA 6541 TTGCAGCTTA 6541 TTGCAGCTTA 6541 TTGCAGCTAG 6541 TTGCAGCTAG 6541 TTGCAGCTAG 6541 TCCGCTAGC 6541 CCTGGGGGC 6541 CCTGGGGGC 6721 GAACTGTTA 6721 GAAATGTTAC 6731 GAATTGTAC 6731 GAATTGTAC 6731 GAATTGTAC 6731 CCGGGGGGC 6731 CCGGGGGCC 6731 CCGGGGGCC 6731 CCGGGGGCC 6731 CCGGGGGCC 6731 CCGGGGGCC 6731 CCGCTGGCC 6731 CCGCTGGCC 6731 CCGCTGGCC 6731 CCGCTGGCC 6731 CCGCTGGCC 6731 CCCCTGGCC 6731 CCCCTGGCC 6731 CCCCTGGAG 6731 CCCCTGGA	6181	TTTAATTTGT	AAAGGGGTTA	ATAAGGAATA	TTTGATGTAT	AGTGCCTTGA	CTAGAGATCA
6361 ATARTGETT CARATARAGE ANTAGATECA CARATTECA	6241	TAATCAGCCA	TACCACATTT	GTAGAGGTTT	TACTTGCTTT	AAAAAACCTC	CCACACCTCC
6361 TATATGGTTA CAAATAAAGC AATAGCATCA CAAATTTCAC AAATAAAGCA TTTTTTCAC 6421 TGCATCTTAG TTGTGGTTTG TCCAAACTCA TCAAAGTATC TCATCATGT TGGATCGGCT 6481 GGATGATCCT CCAGCGCGG 6541 TTGCAGCTTA TAATGGTTAC 6541 TTGCAGCTTA TAATGGTTAC 6561 TTTTTTCACT GCATTCTAGT TGTGGTTTCT 6561 GTATACCGTC GCATCTCAGC TAGAGCTTG CCAAACTCAT CAATGTATCT TATCATGTCT 6561 GTATACCGTC GCATCTCAGC TAGAGCTTG CCAAACTCAT CAATGTATCT TATCATGTCT 65721 GAAATTGTAC TCCGCTCACA ATCCACACA ACATACAGAC CGGAAGCAT AAGTGTATAG 6781 CCTGGGGTG CTAATGAGTG AGCTAACTCA CATTAATTGC GTCCATAGCTG TTCCCGTGTG 6841 TCCGCTCACA ATCCACACA ACATACAGAC CGGAAGCAT AAGTGTAAAG 6781 CCAGCGGGGA CAACCTCTGG TGCCAGCTC CATCACACACA ACATACAGC CGGAAGCAT AAGTGTAAAG 6781 CCAGCGGGGA CAACCTCTGGG TCCTCCCCTC CAAAGGCC CGCAAAGGC CGCAGAGAGAAAGACACAAAAAGACACACAC	6301	CCCTGAACCT	GAAACATAAA	ATGAATGCAA	TTGTTGTTGT	TAACTTGTTT	ATTICCACCTUT
6421 GGATGATCT CIAGGGGGG GATCTCATGC TGAATCTATC TATCATGTC TGGATTGGCT 6541 TGCAGCTA TAATGGTAC AAATAAAGCA ATAGCATCA 6561 TTTTTCACT GCATCTAGT TGTGGTTTGT CCAAACTCAT CAATGTTAC 6661 GTATACCGTC GACCTCTAGC TAGAGCTTGG CGTAATCATC CAAATGTATCT TATCATGTCT 6721 GAAATTGTAT TCCGCTCACA ATTCCACCACA ACATACCAGC CGCAAGCATA AAGTTAAAGCA 6781 CCTGGGGTGG CTAATGAGT AGCTACCACA ACATACGAGC CGGAAGCATA AAGTTAAAG 6781 CCTGGGGTGG CTAATGAGT AGCTACCACA ACATACGAGC CGGAAGCATA AAGTTAAAG 6781 CCTGGGGTGG CTAATGAGT AGCTACCACA ACATACGAGC CGGAAGCATA AAGTTAAAG 6781 CCCGGGTGGG CTAATGAGT AGCTACCACA ACATACGAGC CGGAAGCATA AAGTTAAAG 6781 CCCGGGTGGG CTAATGAGT AGCTACCACA ACATACGAGC CGGAAGCATA AGGTTAAAG 6781 CCCGGGTGGG TATTGGGCC TCTCCGGTC CATTAATGAAT CGGCCAACGC CGGGGGAGG 6781 CCCGGGTTGC TATTGGGCC TCTCCGGTC CATTAATGAAT CGGCCAACGC CGCGGGGAGG 6781 CTCGGGTGCG TATTGGGCC TCTCCGGTC CAAAAGGCCA TAATACGGTTA TCCACAGAAT 6841 TCCAGTGCG GCGAGCGGTA TCAGCCACT CAAAAGGCCA TAACAGGTA TCCACAGAAA 6901 CCGCGTTACC CGTCGGGC TTTTTCCCACC CAAAAGGCCA AGCACACGAC 7021 CAGGGGATAA CGCAGAAAG AACATTGAG CAAAAGGCCA AGCACACAA 7021 CCCCTGGAAG CTCCCTCGTG CGCTCTCCTT TTCCGACCCC CTCACGAGCA AGCACCCTA 7201 CCCCTGGAAG CTCCCTCGTG CGCTCTCCTCT TTCCGACCCT CCCCCTGACGAG AGCACCACA 7201 CCCCTGGAAG CTCCTCTGT CCCTTCCTG TTCCGACCCT CCCCCTGACGAG ACACACCTAC 7201 CCCCTGGAAG CTCCCTCGT CCCTTCCTG TTCCGACCCT CCCCCTCAAGCAC 7201 CCCCTGGAAG CCCCTCTCTCGT CCCTTCCTG TTCCGACCCT CCCCCTCAACCACAAA 7441 CCCACCTGC CTTACCCGT CCCAACGCGC CTTACCCAACACACACACACACACACACACACACACAC	6361	ATAATGGTTA	CAAATAAAGC	AATAGCATCA	CAAATTTCAC	AAATAAAGCA	TTTTTTTCAC
6541 TTGCAGCTTA TAATGGTTAC AAATAAAGCA ATAGCATCAC AAATTTCACA AATAAAGCAT 6601 TTTTTTCACT GCATTCTAGT TGTGGTTTGT 6661 GTATACCGTC GACCTCTAGC TAGAGCTTGG CGAAACTCAT CAATGTATCT TATCATGTGT 6721 GAAATTGTAT TCGGCTCACA ATTCCACACA ACATACGAGC CGGAAGCATA AAGTTAAAGCAT 6731 CCTGGGGTGC CTAATGAGTG AGCTACACA ACATACGAGC CGGAAGCATA AAGTTAAAGCAG 6781 CCCGGGGGGGGC CTAATGAGTG AGCTACACCA ACATACGAGC CGGAAGCATA AAGTTAAAG 6841 TCCAGTGGG AAACCTGTCG TGCCAGCTC CATTGAATTGC CTGCCCGGTTC 6841 TCCGGTTGCG CTAATTGGGCG CTCACCACA ACATACGAGC CGGAACGC CGCGGGGAGAG 6901 GCGGTTTGCC TATTGGGCGC TCTTCCCGCTT CCTCGCTCAC CTGACTCGCT CGCTCGGTCG 6901 TCCGGCTGCG CTAATTGGGCG CTCACCCCT CAAAGGCCA CTGACCGCT CGCTCGGTCC 6901 TCCGGCTGCG CTTGCTGGC CTTTCCCACC CAAAAGGCCA CGCAAAAGGCC AGGAACCGTA 7021 CAGGGGATAA CGCAGAAGA AACATGGAG CAAAAGGCCA CCCCTGAGAGA 7141 ATCGACGCTC AAGTCAGAGG TTGCTCATG CGCCCACCCT GCCCCTGAAG 7261 CCCCTGGAAG CTCCCTCGTG CGCTCCTCTG TCCCACCCT GCCCCTTACC CCCTTCAGGA 7261 CCCCTGGAAG CTCCCTCGTG CGCTCCTCTG TCCCACCCT GCCCCTTACC CCCTTCAGGAC 7261 CCCCTGGAG CTCCCTCGTG CGCTCCTCTG TCCCACCCT GCCCCTC TCCCCTCGGAACC 7261 CCCCTGGAG CTCCCTCGGGA AACTACTCCG TTCCAACCCC GCCCCCC GTTCACCCCC 7381 ACCCGCTTCCC CCCTTCGGGA ACCGGCTACCT TCCAACCCT GCCCCCC GTTCACCCCC 7381 ACCCGCTTCGC ACCACCACT ACCAACACAAA 7441 ACCGCTCGCC CTTACCCGGT AACTACTCG CCTACCCCC GTTCAGCCCC 7561 CGCCTCTCT GAACCAGT ACCATCTTT CTCATCACACC TAACCAGAC ACCACTTAT 7601 CAAATTAAAA ATGAAGTTT AAATCATT TTTCAACAACA CCCGGTAAACA 7681 AAACCACCCC TGGTACCGGT TTCACTCTT TCACCACCT TAACCACTAC AGCAGATTAC GCCCCAAAAAA 7681 AAACCACCCC TGGTACCGGT TTCACCACCA AAAGAGTTTAC TTGCACCAACAAA 7681 CACCACCAC AGAAGCCACT TCCATCCGGAACAAAAA 7681 AAACCACCCC CGGAACCAC TCCATCCTGT TTGACTCTAATCAG TAACCAACAAAAAAAAAA	6421	TGCATTCTAG	TTGTGGTTTG	TCCAAACTCA	TCAATGTATC	TTATCATGTC	
6541 TTGCAGCTTA TAATGGTTAC AAATAAAGCA ATAGCATCAC AAATTTCACA AATAAAGCAT 6601 TTTTTTCACT GCATTCTAGT TGTGGTTTGT 6661 GTATACCGTC GACCTCTAGC TAGAGCTTGG CGAAACTCAT CAATGTATCT TATCATGTGT 6721 GAAATTGTAT TCGGCTCACA ATTCCACACA ACATACGAGC CGGAAGCATA AAGTTAAAGCAT 6731 CCTGGGGTGC CTAATGAGTG AGCTACACA ACATACGAGC CGGAAGCATA AAGTTAAAGCAG 6781 CCCGGGGGGGGC CTAATGAGTG AGCTACACCA ACATACGAGC CGGAAGCATA AAGTTAAAG 6841 TCCAGTGGG AAACCTGTCG TGCCAGCTC CATTGAATTGC CTGCCCGGTTC 6841 TCCGGTTGCG CTAATTGGGCG CTCACCACA ACATACGAGC CGGAACGC CGCGGGGAGAG 6901 GCGGTTTGCC TATTGGGCGC TCTTCCCGCTT CCTCGCTCAC CTGACTCGCT CGCTCGGTCG 6901 TCCGGCTGCG CTAATTGGGCG CTCACCCCT CAAAGGCCA CTGACCGCT CGCTCGGTCC 6901 TCCGGCTGCG CTTGCTGGC CTTTCCCACC CAAAAGGCCA CGCAAAAGGCC AGGAACCGTA 7021 CAGGGGATAA CGCAGAAGA AACATGGAG CAAAAGGCCA CCCCTGAGAGA 7141 ATCGACGCTC AAGTCAGAGG TTGCTCATG CGCCCACCCT GCCCCTGAAG 7261 CCCCTGGAAG CTCCCTCGTG CGCTCCTCTG TCCCACCCT GCCCCTTACC CCCTTCAGGA 7261 CCCCTGGAAG CTCCCTCGTG CGCTCCTCTG TCCCACCCT GCCCCTTACC CCCTTCAGGAC 7261 CCCCTGGAG CTCCCTCGTG CGCTCCTCTG TCCCACCCT GCCCCTC TCCCCTCGGAACC 7261 CCCCTGGAG CTCCCTCGGGA AACTACTCCG TTCCAACCCC GCCCCCC GTTCACCCCC 7381 ACCCGCTTCCC CCCTTCGGGA ACCGGCTACCT TCCAACCCT GCCCCCC GTTCACCCCC 7381 ACCCGCTTCGC ACCACCACT ACCAACACAAA 7441 ACCGCTCGCC CTTACCCGGT AACTACTCG CCTACCCCC GTTCAGCCCC 7561 CGCCTCTCT GAACCAGT ACCATCTTT CTCATCACACC TAACCAGAC ACCACTTAT 7601 CAAATTAAAA ATGAAGTTT AAATCATT TTTCAACAACA CCCGGTAAACA 7681 AAACCACCCC TGGTACCGGT TTCACTCTT TCACCACCT TAACCACTAC AGCAGATTAC GCCCCAAAAAA 7681 AAACCACCCC TGGTACCGGT TTCACCACCA AAAGAGTTTAC TTGCACCAACAAA 7681 CACCACCAC AGAAGCCACT TCCATCCGGAACAAAAA 7681 AAACCACCCC CGGAACCAC TCCATCCTGT TTGACTCTAATCAG TAACCAACAAAAAAAAAA	6481	GGATGATCCT	CCAGCGCGGG	GATCTCATGC	TGGAGTTCTT	CGCCCACCCC	AACTTGTTTA
6661 GTATACCETC GACCTCTAGC TAGAGCTEG CAAACTCAT CAATGATCT TATCATGTCT 6721 GAAATTGTTA TCCGCTCACA ATTCCACACA ACATACAGAG CGGAAGCATA AAGTTAAAAG 6781 CCTGGGGTGC CTAATGAGT GCCAACACA ACATACAGAG CGGAAGCATA AAGTTAAAAG 6781 CCTGGGTGC CTAATGAGT ACCTTACTCACACA ACATACAGAG CGGAAGCATA AAGTTAAAAG 6781 TCCAGTCGG 6841 TCCAGTCGGG 6901 GCGGTTTGGG TATTGGGCGG TTTCCGGTT CCTCGGCTCAC 67901 GCGGTTTGGG GCGAGAGAAG ACATACAGAG CAAAAGGCCA 6901 TTGGGCTGG GCGAGAGAAG ACATACAGAC CAAAAGGCCA 7021 CAGGGGATAA CCGCAGGAAAA AACATCTGAA GGCTCACCT 7021 CAGGGGATAA CCCCAGGAAAA AACATCTGAA GGCAAAAAGGCCA 7021 CCCCTGGAAG CTCCCTCGT GCCCTCTCT 7021 CCCCTGGAAG CTCCCTCGT GCCCTCTCT 7021 CCCCTGGAAG CTCCCTCGT GCCCTCTCT 7021 CCCCTGGAAG CTCCCTCGT CCCTCTCT 7021 CCCCTGGAAG CTCCCTCGT CCCTCTCT 7021 CCCCTGGAAG CTCCCTCGT CCCTCCGT CCCCCTCGAAAAAGGCCA 7021 CCCCTGGAAG CTCCCTCGT CCCTCCTCT 7021 CCCCTGGAAG CTCCCTCGT CCCTCCGT CCCTCCGT CCCCCTCGAAAAAGGCCA 7021 CCCCTGGAAG CTCCCTCGT CCCTCCGT CCCTCCGT CCCCCCTCACACAAAA 7021 CCCCTGGAAG CTCCCTCGT CCCTCCGT CCCTCCTCT CCCCCCTCGAAAAAGACCCAC CCCGCTAACACAAA 7021 CCCCTGGAAG CTCCCTCGT CCCTCCGT CCCTCCGT CCCCCCTCCCT	6541	TTGCAGCTTA	TAATGGTTAC	AAATAAAGCA	ATAGCATCAC	AAATTTCACA	AATAAAGCAT
6661 GTATACCGTC GACCTCTAGC TAGAGCTTGG CGTAATCAGG GTCATAGGTG TTTCCTGTGTGT 6721 GAAATTGTTA TCCGCTCACA ATTCCACACA ACATACGAGC GGGAAGCATA AAGTGTAAAAG 6781 CCTGGGGTGC CTAATGAGTG AGCTAACTCA CATTAATGCAGC GGGGCAAGCG CGGGGGAGG 6841 TCCAGTCGG TATTGGGCG TCTTCCGGTC CTTCCGCTCAC TGCCCGCCTC 6961 TTCGGCTGCG GCGAGCGGTA TCAGCTCACT CAAAAGGCGGT AATTACGAGC GCGGGAGAGA 7021 CAGGGGATAA CGCAGGAAAA AACATCTGAC CAAAAGGCGT AATAACGAGCA 7141 ATCGACGCT CAAGTGGG GTTTTCCCATA GGCCCCCCCCCC	6601	TTTTTTCACT	GCATTCTAGT	TGTGGTTTGT	CCAAACTCAT	CAATGTATCT	TATCATGTCT
6781 CCTGGGGTGC CTAATGAGTG AGCTAACTCA CATTAATGG CGGAAGCATA AAGTGTAAAG 6781 TCCGGTGGG AAACCTGTCG 6841 TCCAGTCGG AAACCTGTCG 6841 TCCAGTCGG AAACCTGTCG 6841 TCCAGTCGG AAACCTGTCG 6861 TTCGGCTGC TATTGGGCGC TCTTCCGCTT 68661 TTCGGCTGC GGGAGCGGTA TCAGCTCACT CTCCCCTCACT TGCCTACCT 6861 TTCGGCTGCG GGGAGCGGTA TCAGCTCACT CAAAGGCCG TAGACTCGGTC 6702 CAGGGGATAA CGCAGAAAG AACATGTAG CAAAAAGGCCA GCAAAAAGCCA 7021 CAGGGGATAA CGCAGAAAG AACATGTAG CAAAAAGGCCA GCAAAAAGCCA 7081 AAAAGCCCG TTGCTGGGG TTTTTCCATA GGCTCCGCC CCCTGACGAG CATCACAAAA 7141 ATCGACGCCT CAGTCAGAGG TGGCCGAAACC CGCACAGACT ATAAAGATAC CAGCCGTTTC 7261 CCCCTGGAAG CTCCTCTGT TTCCGACCT GCCGCTTACC GAATACCTA 7221 GTTCGGTGTA GGTCGTTCGC TCCAGAGCG TTTCTCAATG CTCACGCTGT AGGTACCTCA 7221 GTTCGGTGTA GGTCGTTCCG TCCAGAGCG TTTCTCAATG CTCACGCTGT AGGTACCTCA 7221 GTTCGGTGTA GGCGTTCCC TCCAGACGTG CTCACACCAC CCCCGTTAACA 7221 GTTCGGTGTA GGCGTTCCC TCCAACGAGG CAGACCCCCC GTTCAGCCCG 7381 ACCGCTGCC CTTATCCGGT AACTATCGTC TTGAGTCCAA CCCGGTTAACA 7441 CGCCACTGC AGCAGCACT ACCTTCCGT AACTATCGTC TTGAGTCCAA CACGACTTAT 7501 CAGAGTTCTT GAAGCGAGT ACCTTCCGGA AACTATCGTC 7561 GCGCTCTGCT GAAGCCAGTT ACCTTCGGAA 7621 AAACCACCCC TGGTAGCGGT TTTTTTG TAGCAGAGC GAGGATTACG 7621 AAACCACCC TGGTAGCGGT TTTTTTTG TTTGCAAGCA GCAGACTTAT 7661 AAGGATCTCA AGAAGATCCT TTGATTTTTT TTTGCAAGCA GCAGATTACG CCCGGAAAAA 7741 ACTCACGTTA AGGAGATCTT TGATCTTTTT TTAGCAGGGTC TGACCCTCAG TGACGCAAC 7861 TAAATAAAA AAGAAGTCCT TTGATCATTT TAACGGGGTC TGACCCTCAG TGACCCACA 7861 TAAATAAAA ATGAAGTTTT AAATCAATCT AAAGTAATATA TGAGTAAACT TGAGCACAACA 7861 TAATTAAAA ATGAAGTTTT AAATCAATCT AAAGTAATATA TGAGTAAACT TCGTCTAACCACACA 7861 CACGCCACC GGAAGGACC GGAGACCCAC GCCAGATTAAT TCGCTCAACCAA 7861 ACCTTCTTTAC CATTGCTAC GAACCACCA TCTCACCCAG TCCACCACCA 7861 ACCACCACC GGAAGGACC GAAGCCACA TCTCACCCAC TCCACCATT TCCACCACAA ACCAACTAACCACACA TCCACCAACAA TCAACGACAA TCAAGAGACC AACAATAA TCAGCTTCAC GCCAATAAA 7741 ACTCACTTACA ACCAACTACA TCTCACCACA ACCAACTA TCTCACCACAAAAACCACACC CATTGCTACA AACACTACTACA TCCACCACA TCCACCAACAAAAACACACAC	6661	GTATACCGTC	GACCTCTAGC	TAGAGCTTGG	CGTAATCATG	GTCATAGCTG	TTTCCTGTGT
6781 CCTGGGGTGC CTAATGAGTG AGCTAACTCA CATTAATTGC GTTGCGCTCA CTGCCCGCTT 6841 TCCAGTCGGG AAACCTGTCG TGCCAGCTGC ATTAATGAT CGGCCAACGC 6961 TTCCGGCTGC GCGAGCGGTA TCAGCTCACT CCTCGCTCAC TGACTCGCTC 6961 TTCGGCTGCG GCGAGCGGTA TCAGCTCACT CAAAGGCGGT AATACGGTTA TCCACAGAAT 7021 CAGGGGATAA CGCAGCAGAAGA AACATTGAGC CAAAAGGCCA GCAAAAGGCC AGAACCGTA 7081 AAAAGGCCC GTTGCTGGCG TTTTTCCATA GGCTCCGCCC CCCTGACGAG CATCACAAAA 7081 AAAAGGCCC GTTGCTGGCG TTTTTCCATA GGCTCCGCCC CCCTGACGAG CATCACAAAA 7081 AAAAGGCCC GTTGCTGGCG TTTTTCCATA GGCTCCGCCC CCCTGACGAG CATCACAAAA 7081 AACGCACGCT CAAGCAGGA CCCCCTCGTG CGCTCTTCCTG TCCGACCCCT GCCGCTTACC GGATACCTGT 7201 CCCCTGGAAG CTCCCTCGTG CGCTCTTCCTG TCCGACCCCT GCCGCTTACC GGATACCTGT 7201 CCCCTGGAAG CTCCCTCGTG CGCTCTTCCTG TCCGACCCCT GCCGCTTACC GGATACCTGT 7201 CCCCTGGAAG AGCGTGGCG TTTCCAACTAG CCCAGCTTAT 7201 CGCCATGGC CTATCCGGT AACTATCGTC TGAGTCCAA CCCGGTAACA 7201 GTTCGGTGTA GGCGATACCAGG TTCCAACCTGT ACCTTGTGATCCAT 721 GTTCGGTGTA GGCAGCCACT GCTAACTACG GCTTGAGCCCC GTTCAGCCCC 7281 AACCACTGC AGCAGCACT AACTAACGAC GCTACACTAA 7281 CGCGCTCTGCT GAAGCCACT ACCTTCGGAA AAAAGAGTTG TAGGCACTAA TTTGGTATCT 7281 AAACCACCGC TGGTAGCGGT GGTTTTTTTG TTGCAAGCA GCAGATTAC CCGCGAAAAA 7281 AACCACCGC TGGTAGCGGT GGTTTTTTTT CTACAGGGT TAGGCCTCAG TGGAAACAAA 7281 AACCACCGC TGGTAGCGGT GGTTTTTTTT CTACAGGGT TAGGCCTCAG TGGAAACAAA 7281 AACCACCAC AGAAGATCCT TTGATCTTTT CTACAGGGT TAGACCTCAC TGGAACAAAA 7281 CACACCACGC TAAACCAC GGAGCCCCA TTAAACAATA TAAAAAAAA GAAGATTTT AAAACAATCA TAAAAAAAA GAAGATTTT AAAACAATCA TAAAAAAAA GAAGATTAT TCAGCAACAAAA 7281 CACACGCTC AATCACAT GAAGCACCCAC GTGAACAAAA TTACAACAAAA GAACATCATT AAAACAATCA TAAACAATAA TAACAATAA CACAACCACC GGAAGGCCC GAACGCCC GAACGCCC GAACGCCC TAACACACC GGAAGGCC CAACAACAC CCAACTGTT TAACACAACA GAAGATCAA CAACACACCAC TAACACACC CAACAACAC CAACACCAC CAACACACC CAACACAC TAACACACC CAACACAC CAACACCAC CAACAC	6721	GAAATTGTTA	TCCGCTCACA	ATTCCACACA	ACATACGAGC	CGGAAGCATA	AAGTGTAAAG
6841 TCCAGTGGG AAACCTGTCG TGCCAGCTGC ATTAATGAAT CGGCCAACGC GCGGGGAGA GPO1 TCCGCTTCGCTT CCTCGCTT CCTCGCTCAC TGACTCGCTG CGCTCGGTCG GCGAGCGTA TCAGCTCACT CAAAGGCGGT AATACGGTTA TCCACAGAAT TO21 CAGGGGATAA CGCAGAAAGA CACATGTGAG CAAAAGGCCA GCAAAAGGCC AGGAACCGTA TTTTCCATA GGCTCCCCTGGAGC CCCTTGACGAG CACCACAGAAC CCCCTGGAGAC CCCCTGGAGAC CCCCTTGACGAG CTCCCTCGTG CCCCTCGGGA AGCTCCTCCT CCCTCGGAG CTCCCTCGTG CCCCTTGAGAC CCCCCTGAGAC CAAAAGGCCA AAACATGTCA CCCCTTGACAAAA ACCATGTCAC CCCCTGAACAC CAAAAGGCCA AAAAAAGGCCA AACTATCACACAAAAA ACCATGTCA CCCCTTGACACA AACTATCGTC TCCACAGAAC CCCCCTGACGAG CATCACAAAAA ACCATGTCA CCCCTTGACGAG CTCCCTCGGA ACCTCCTCTCT CCCTCGGAA ACCTACCTC TTCCAACCT CCCTTCAGC CCTTACCAGC CTTATCCGGT ACCTACACTA CACCACCAC CTTATCCGGT ACCTACACTAC CCACACAGAC CCCGGTAAGA CACCACCT TTCAATCGT CACACACAC CCCGGTAAGA CACCACCTTATCGGAACCAC CCTAACACAC CCCACAGACCAC CCTAACACAC CCCACAGACCAC CCTAACACAC CCCACAGACCAC CCCACACGAC CCCACACACA	6781	CCTGGGGTGC	CTAATGAGTG	AGCTAACTCA	CATTAATTGC	GTTGCGCTCA	CTGCCCGCTT
6901 GCGGTTTGCG GCGAGCGGTA 7021 CAGGGGATAA 7081 AAAAGGCCGC GTTGCTGGCG 7141 ATCGACCCC 7141 ATCGACCCC 7141 ATCGACCCC 7150 CCCCTGGAAG 7151 CCCCTGGAAG 7151 CCCCTTGGAAG 7151 CCCCTTGGAAG 7151 CCCCTTCGGAA 7151 CCCCCTTCGGAA 7151 CCCCTTCGGAA 7151 CCCCTTCGGAA 7151 CCCCCTTCGGAA 7151 CCCCTTCGGAA 7151 CCCCTTCGGAAACCACT 7151 CCCCTTCGGAAACCACT 7151 CCCCTTCGGAAACCACT 7151 CCCCCTTCGGAAACCACT 7151 CCCCTTCGGAAACCACT 7151 CCCCTTCGGAAACCACT 7151 CCCCCTTCGGAAACCACT 7151 CCCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCCTTCCTC 7151 CCCCCTCCTCTC 7151 CCCCCTTCCTC 7151 CCCCCTCCTCTC 7151 CCCCCTCCTCTC 7151 CCCCCCTCCTCTC 7151 CCCCCCTCCTCTC 7151 CCCCCCTCCTCTC 7151 CCCCCCTCCTCTC 7151 CCCCCCTCCTCTC 7151 CCCCCCCTCCTCTCTC 7151 CCCCCCTTCCTC 7151 CCCCCCCTCCTCTCTC 7151 CCCCCCCTCCTCTCCTC 7151 CCCCCCTCCTCTCCTC 7151 CCCCCCTCCTCTCTCTC 7151 CCCCCCCTCCTCTCTCC 7151 CCCCCCTCCTCTCCTC 7151 CCCCCCTCCTCTCTCC 7151 CCCCCCTCCTCTCTCC 7151 CC	6841	TCCAGTCGGG	AAACCTGTCG	TGCCAGCTGC	ATTAATGAAT	CGGCCAACGC	
7021 CAGGGATAA CGCAGGAAG AACATGTGAG CAAAAGGCCA AGGAACGTAA TORA AAAAAGGCCA AGGAAAGC CATCACAAAA ACATGTGAG GCAAAAGGCCA AGGAACCAAAAA ACATGTGAG GCACCAGACCAAAAA ACATGTGAG GCACCAGACCAAAAA ACATGTGAG GCACCACAAAAA ACATGTGAG GCACCACAAAAA ACATGTGAG GCTCCCCTCGT TTCCGACCCT GCCCTTACC GCACCAGACC CCCTGACGAG GCCCTTACC GCCCTTTCC CCCTTCGGGA AGCAGCCCCT TTCCGACCCT GCCGCTTACC GGAACCCCC GCCCTTACC GGAACCTCCT TTCCGACCCT GCCGCTTACC GGAACCCCC GTTCAGCCGA AGCAACCCCC GTTCAGCCGA AGCAGCCACC GCCTTACC GCCGTTACC GGAACCCCC GTTCAGCCGA ACCTACTACG CTCACCGCTG AGCAACCCCC GTTCAGCCGA ACTACTACGA TTAGCAGAGA CACGGACTACA GCCGGTAACA CACGACTTAC TAGCACCTC GAAGCCACT GCCACACCAC GCACCACCAC GCACCACCAC GACACCCCC GTTCAGCCGA AACACCACCAC GACACCCCC GTTCAGCCGA AACACCACCAC GACACCACCAC GCACACCAC GCACACCAC GCACACCAC GACACCCCC GTTCAGCCGA AAACACCACCAC GACACCACCAC GCACACCAC GCACACCACAC GCACACCAC CTACCACGAC AACACCACC CACCACCAC GCACACCAC CCACCACCAC GCACACCAC GCACACACCAC GCACACACCAC GCACACACCAC GCACACACCAC GCACCACCAC GCACACACCAC GCACACACCAC GCACACACCAC GCACACACCAC GCACACACA	6901	GCGGTTTGCG	TATTGGGCGC	TCTTCCGCTT	CCTCGCTCAC	TGACTCGCTG	CGCTCGGTCG
7081 AAAAGGCCG GTTGCTGGCG TTTTTCCATA GGCTCCGCC CCCTGACGAG AGAACCGTA 7141 ATCGACGCT AAGTCAGAGG TGGCGAAACC CGACAGGACT ATAAAAGATAC CAGGCGTTTC 7201 CCCCTGAGAG CTCCCTCGTG CGCTCTCTG TTCCGACCCT GCCCCTGACGAG CATCACAAAA 7121 GTTCGGTGTA GCTCCTCGGA AGGCTGGCGC TTTCCAATG CTCACGCTTT 7261 CCGCTTTCT CCCTTCGGGA AGGCTGGCGC TTTCCAATG CTCACGCTGT AGGTATCTCA 7321 GTTCGGTGTA GGTCGTCCCC TCCAAGCTGG GCTGTGTGCA CGAACCCCCC GTTCAGCCCG 7381 ACCGCTGCC CTTATCCGGT AACTATCGTC TTGAGTCCAA 7441 CGCCACTGGC AGCAGCCACT GGTAACAGGA TTAACAGAGA CACGACTTAT 7501 CAGAGTTCTT GAAGTGGTGG CCTAACTACG GCTACACTAG GAGGACACTC GAAGCACCCCC GTTCAGCCCG 7561 GCGCTCTGCT GAAGCCACT GCTAACACGG GAGGTATGTA GGCGGTACTA 7501 CAGAGTTCTT GAAGTGGTGG CGTAACACAC GCTACCTAG GAGGCAGTA TTTGGTATCT 7561 GCGCTCTGCT GAAGCCACT TTGATCTTTT CTACCAACCA 7681 AAACCACCGC TGGTAGCGGT GGTTTTTTTT TTTGCAAGAC GAGACACTA TTTGGTATCT 7681 AAACCACCGC TGGTAGCGGT GGTTTTTTTT TTTGCAAGAC GCAGATTACG CGCAGAAAAA 7681 AAACTAATAAA ATGAAGTTTT AAATCATCT TAACCATAC GCAGATTACA GAGACCCCC TAGATCCTAT 7861 GTTACCAATG CTTAATCAGT GAGCCACCTA TCTCAGCGGT TGACGCTCAC TGACCTCTT 7801 TAAATTAAAA ATGAAGTTTT AAATCAATCT TCTCAGCGGT TTTCCACCATC 7981 CCAGTGCTG AATGATACCG CGAGAACCCCC GTTCACCGGC TTCCAGCGCT TCCAGACTAC GCCAGCTATAC GTTCATCCACCACCA AATGATACCG CGGAAGCCCCC GTTCACCGGC TCCACCGGC TCCACCGC TCCAGCACACA AATGATACCG CGAGACCCCC GTTCACCGGC TCCACCGGC TCCACCGC TCCAGCACTA TCCAGCATTA ACTTTCACCA 8041 ACCAGCCACC CATTGCTACA GGCATCGTG TTCACCACTAC GCCAGTTTAT TCAGCAATAA 8041 ACCAGCACC CATTGCTACA GGCATCGTG TTCACACTAC GCCAGTTTAT TCAGCAATAA 8041 ACCAGCACCC CATTGCTACA GGCATCGTG TTCACACTAC GCCAGCTTAT TCAGCCACCA 8101 AGCTTTTATA TTGTGCCG GAAGCCCCC GAAGCCACC TTCAAGAGATAA TTGAGCTCCC TCCAACGA TTAAATCCC CCGACCATA TCACGATTA ACTTTCACCA 8221 TCAGCTCCGG TCCCAACA TCAGAGTAA GTTGCCCC GCCACATATA ACTTTCACCA 8221 TCAGCTCCGG TCCCAACA TCAGAGTAA GTTGCCCC GCCACATATA ACTTTCACCA 8221 TCAGCTCCGG TGAGCAATA CCAGCACA TTAAATCCC TTACCACACA TTAAATCCC CCATCCTAC ACCAACATA TTAAAAAAAGGCA TTAAATCCC CCACCAA AAAAAAAGGCA AAAACGCCCC TTCCAACACA TTAACCCACCAA AAACCTCCCA AAAACAGGAAAA ACAGGAAAAA ACAGGAA	6961	TTCGGCTGCG	GCGAGCGGTA	TCAGCTCACT	CAAAGGCGGT	AATACGGTTA	TCCACAGAAT
7081 AAAAGGCCGC GTTGCTGGCG TTTTTCCATA GGCTCCGCC CCCTGACGAG CATCACAAAA ATCAGACGCTTTC CAGGCGTTTC CCCCTGGAAG CTCCCCTCGTG TGCCGAAACC CGACAGCAT ATAAAGATAC CAGGCGTTTC CCCTTCGGAA GCCCCTCCTG TTCCCGACCCT GCCGCTACC GGATACCACAAAA ACAGGACTTAT CCCCTTCGGAA ACCACCCCG TTTCCCAACCTG CCCTTCCTG TTCCCGACCCT GCCGCTTACC GGATACCACAAAA ACAGGAACTATA CTCCACCCGC CTTATCCGGA ACCACCTGG TTCCAAGCTG CCCGGTAAGA CACGACTTAT CCCCACCCG AACCACCTG GTAACAACAGA TTAGACAGAC CAGGCTATAT CCACACACCACT GGTAACAACAGA TTAGACAGAC CAGGCTATAT TTCCCAACCTG GAACCACCT GAACCACCT GAACCACCT GAACCACCT GAACCACCT GAACCACCT GAACCACCT GAACCACACT TTCACCACTAC AACGACTTAT TCCGGCAAAAC CACGACTTAT ACCTTCCGGA AAACCACCCC TGGTAGACACACAC GCCACTACACACA CACGACTTAT TCCGGCAAACACACACCT TGGTAGCACACACACACACACTTAT TCCGGCAAAAC ACCACCTTAT TCCGGCAAAAC ACCACCTTAT TCCGGCAAAAC ACCACCTTAT TCCGGCAAAAC ACCACCTTAT TCCGGCAAAAC ACCACCTTAT TCCGGCAAAAC ACCACCTCT TTGATCTATT TCCACACACACACACACACACACACACACACA	7021	CAGGGGATAA	CGCAGGAAAG	AACATGTGAG	CAAAAGGCCA	GCAAAAGGCC	AGGAACCGTA
7201 CCCCTGGAGG CTCCCTCGTG CGCTCTCCTG 7201 CCCCTGGAGAG CTCCCTCGTG CGCTCTCCTG 7201 CCCCTTGGAGAGC CTCCCTCGTG CGCTCTCCTG 7201 CCCCTTGGAGA ACCGTGGCGC TTTCCGACCT GCCGCTTACC GGGATACCTGT 7201 CCCCTTGGGA AGCGTGGCGC TTTCCTAATG CTCACGCTGT AGGTACCTGT 7321 GTTGGTGTA GGTCGTTCCGT ACTATCCGT TTGAGTCCAA CCGGTAAGA CACGACTTAT 7441 CGCCACTGGC AGCACCACT GGTAACAGGA TTTAGCAGAGC GAGGTATGA GCGGTGCTA 7501 CAGAGTCTT GAAGCCACT GAACCACCT GGTAACAGCA GAGGTATGA GCGGTGCTA 7501 CAGAGTCTT GAAGCCACT ACCTTCGGAA ACACACTCATG AAGGACAGTA TTTGGTTAT 7501 CAGAGTCTCT GAAGCCACT ACCTTCGGAA AAAAAGAGTTG TAGCAGAGC GAGGTATGA GCGGGTATAC 7621 AAACCACCGC TGGTAGCAGT ACCTTCGGAA AAAAAGAGTTG TAGCACACA GCGAACAAC 7621 AAACCACCGC TGGTAGCAGT ACCTTCGGAA AAAAGAGTTG TAGCACACA GCGAATAACA 7681 AAGGATCTCA AGAAGATCCT TTGATCTTTT CTCAACCAA GCAGATTACG CGCAGAAAAA 7741 ACTCACGTTA AGGGATTTTG GTCATGAGAT TTTTCAACCAA GCAGATTACG CGCAGAAAAA 7741 ACTCACGTTA AGGGATTTTG GTCATGAGAT TATCAAAAAG GATCTTCACC TAGATCCTTT 7801 TAAAATAAAAA ATGAAGTTTT AAATCAATCA TAAAGTATATA TGAGTAAACT TGGTCCACAC 7921 TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTCACGATACA CTGTCTATTT CGTCCATCA 7921 TAGTTGCCTG AATGATACCG GAGGACCCAC GCTCAACCAC CCGACAATAA CTCACCAGC CCGAAGACCAC CGGAAGCCCAC GCTCAACCAC CCGACACACA TCTCACCGGC TCCAGATTA TCAGCCAATAA 8041 ACCAGCACGC CGGAAGGCCC GAGGCACCAC GCTCACCGCC TCCAGATTAA TCAGCAATAA 8041 ACCAGCACC CCGAAGGGCC GAGCCCACA TAGCAGACTAA AGTTTGCCCA 8101 AGTCTATTAA TTGTTGCCGG GAGCCCACA TAGAGACTAC GCCTCCATCC 8221 TCAGCTCCG TCCCAACCA TCAAGGCGAGA TTAAAACGTC GCCCCATTCCA 8221 TCAGCTCCG TCCCAACCA TCAAGGCGAGA TTAACATCATC CCCAGTTAAT AGTTTCCCCA 8221 TCAGCTCCG TCCCAACCA TCAAGGCGAA TTCTCACCAC TCCAGATTAA AGTTTGCCG 8221 TCAGCTCCG TCCGAACCA TCCGACCAC TCCAGATCTT TCCAGAAAAAA GTTTGCCCC 8341 TCATCTTGC CGGCTCAATA CCGGATAATA CCGCCCACA TAGCAGAACT TTGCAAAAAAAA CCAAGATCTT TCTGAGAACA TTGCACAAAAAAAAAA	7081	AAAAGGCCGC	GTTGCTGGCG	TTTTTCCATA	GGCTCCGCCC	CCCTGACGAG	CATCACAAAA
7261 CCCCTGGAAG CTCCCTGGG AGCGTGGCG TTCCGACCCT GCCGCTTACC GGATACCTGT 7261 CCGCCTTTCT CCCTTCGGG AGCGTGGCG TTTCTCAATG CTCACGCTGT AGGTATCTCA 7321 GTTCGGTGTA GGTCGTTCGC TCCAAGCTGG GCTGTGTGCA CGAACCCCCC GTTCACCCG 7381 ACCGCTGCG CTTATCCGGT AACTATCGTC TTGAGTCCAA 7441 CGCCACTGGC AGCAGCACT GGTAACAGGA TTAGCAGAGC GAGGTATGTA GGCGGTGCTA 7501 CAGAGTTCTT GAAGTGGTG CCTAACTACG GCTACACTAG AAGGACAGTA TTTGTATCT 7561 GCGCTCTGCT GAAGCCAGTT ACCTTCGGAA AAAGAGTTGG TAGCCTTGA TCCGGCAAAC 7621 AAACCACCGC TGGTAGCGGT GGTTTTTTG TTTGCAAGCA GCAGATTACG CGCAGAAAC 7621 AAACCACCGC TGGTAGCGGT TTGATCTTTT TTTGCAAGCA GCAGATTACG CGCAGAAAC 7621 AAACCACCGC TGGTAGCGGT TTGATCTTTT TTTTGCAAGCA GCAGATTACG CGCAGAAAC 7621 AAACCACCGC TGGTAGCGGT TTGATCTTTT TTTTCAAGAAGA GAACCTCAC TGGAACCAAA 7641 ACCTCACGTTA AGGGATTTTG GTCATGAGAT TATCAAAAAA GAACCATTT AAATCAATCT TACACAAAAA ATGAAGTTTT AAATCAATCT TACACAAAAA GAACCAATT TGGTCCACA 7861 GTTACCAATG CTTAATCAGT GAGGCACCAC GCTCACCGGC TCCAGATTAC CTGGTCCACA 7861 GTTACCAATG CTTAATCAGT GAGGCACCAC GCTCACCGGC TCCAGATTAT TCGGTCCACA 7861 CCAGTGCTGC AATGATACCG CGAGCCCAC GCTCACCGGC TCCAGATTAT TCGGTCACA 7861 CCAGTGCTGC CATGATACCG CGAGCCCAC GCTCACCGGC TCCAGATTAT TCGGTCCACA 8041 ACCAGCCAGC CGGAAGGGCC GAAGCCCAC GCTCACCGGC TCCAGATTAT TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAAGCCCAC GCTCACCGGC TCCAGATTAT TCAGCAATAA 8041 ACCTTTTGC CATTGCTCAC GGCATCGTG TTAATCAG GCCTCCATCC 8101 AGTCTATTAA TTGTTGCCG GAAGCTACAG TTAATGATC CCCCATTTT TCGCCAATAC 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGA TTAACTGATC CCCCATTTT TCGCCAATAC 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGA TTACATGATC CCCCATTTT TCGCCAAAAAAA 8281 CGGTTAGCT CTTCGGTCCT CCGATCGTTG TCAAGAAGTAA GTTGGCCCCAACT TCAGAGCTAC TCAGAGCTAC CCCCATTTTT TCGCCAAAAAAAAAA	7141	ATCGACGCTC	AAGTCAGAGG	TGGCGAAACC	CGACAGGACT	ATAAAGATAC	CAGGCGTTTC
7321 GTTCGGTGTA GGTCGTCGC TCCAAGCTGG GCTGTGTCA CGAACCCCC GTTCAGCCCG 7381 ACCGCTGCG CTTATCCGGT ACCTATCTCA 7441 CGCCACTGCC AGCACCCACT GGTAACAGGA TTAGCAGGAG CCCACTAT 7501 CAGAGTTCTT GAAGTGGTG CCTAACCAGG GGTAACACCCC GTTCAGCCCG 7621 AAACCACCGC TGGTAGCGGT GCTTATTCGAACCAG 7621 AAACCACCGC TGGTAGCGGT GGTTTTTTTG TTGCAAGAG GCAACTATA 7641 ACCACGTTA AGGAATTCTT TGATCTTTT TTGCAAGAG GCAACTATA 7641 ACCACGCTA AGAGATCCT TTGATCTTT TTGCAAGAG GCAACTATA 7661 TAAATTAAAA ATGAAGTTTT AAATCAATCT TAAACTAACA 7661 GTTACCAATG CTTAATCAGT GAGGCACCCAC GTCAACAAAA 76781 CCAGGTGCTG AATGATACCG GAGGCACCCAC GTCACCGGAAAA 7681 TAAATTAAAA ATGAAGTTTT AAATCAATCT TAAACTAATA TGGTCTCACCA 7681 CCAGGTGCTG ACCCCCGTC GTGAAGAAAA ATGAAGTTTT TCAGCAGAAAA 7681 TAAATTAAAA ATGAAGTTTT AAAACAACT TACCAAGAAAAG GATCTTCACC TAGATCCTT 7681 TAGCACAATG CTTAATCAGT GAGGCACCCAC GCTCACCGGA CCTGTCTATCACCA 7681 CCAGTGCTGC AATGATACCG GAGGCACCAC GCTCACCGGC TCCAAGATAA 7681 TAAATTAAAA ATGAAGTTTT AAACTCATT TCAGCGGT TCCAGCCCC 7681 CCAGTTGCC AATGATACCG GAGGCACCAC GCTCACCGGC TCCAGATTAT TCAGCAATAA 7681 TAGCAGAACCCAC GCGAAGACCCAC GCTCACCGGC TCCAGACCCAC 7681 CCAGTTGTGC CATTGCCAC GAAGCCCAC GCTCACCGGC TCCAGACCCAC 7681 CCAGTTGTAC CCGGCAACAC TCCAGAGTAA TTAGCAGAAAAAG 8041 ACCAGCCAC TCCAACGA TCCAAGGA TAACTCATCAC 8101 AGTCTATTAA TTGTTGCCGG GAAGCCCAC GCTCACCGGC TCCAGACCCAC 8101 AGTCTATTAA TTGTTGCCGG GAAGCCCAC GCTCACCGGC TCCAGCCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCCCAC GCCCACAC TCCAGCCCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCCCAC GCCCAGATTAAT AGTTTGCGCA 8221 TCAGCCCCG TCCAACGA TCCAAGGAG TAACTCTCAG GCCACTATAT AGTTTCAGCCA 8221 TCAGCTCCGG TCCAACGA TCCAAGGAG TTACATTATCAG GCCATCCGTA AGATCTTCAC 8221 TCAGCTCCG TCCAACGA TCCAGAGTAA TCCAGAGATAA TTCACAGGATA 8221 TCAGCTCCG TCCAACGA TCCAGAGTAA TCCAGCACCAC TCCAGAGTA TTCACAGGATA TTCACAGAAAAAAAAAA	7201	CCCCTGGAAG	CTCCCTCGTG	CGCTCTCCTG	TTCCGACCCT	GCCGCTTACC	GGATACCTGT
7321 GTTCGGTGTA GGTCGTCGC TCCAAGCTGG GCTGTGTGCA CGAACCCCC GTTCAGCCCG 7381 ACCGCTGCGC AGCAGCACT AACTATCGTC TTGAGTCCAA CCCGGTAAGA CACGACTTAT 7441 CGCCACTGGC AGCAGCCACT GGTAACAGGA TTAGCAGGAG GAGGCATTAT 7501 CAGAGTTCTT GAAGTGGTGG CCTAACTACG GCTACACTAG 7561 GCGCTCTGCT GAAGCCAGT ACCTTCGGAA AAAGAGACTA TTTGGTATCT 7621 AAACCACCCC TGGTAGCGGT ACCTTCGGAA AAAGAGACTA TTTGGTATCT 7681 AAGCACCCCC TGGTAGCGGT GTTATCTGT TTTGCAAGCA GCAGATTACC GCCAGAAAA 7741 ACTCACGTTA AGGGATTTT GTCATCAGTT TTTGCAAGCA GCAGATTACC GCCAGAAAA 7741 ACTCACGTTA AGGGATTTT GTCATCAGTT TTTGCAAGCA GCAGATTACC GCCAGAAAA 7741 ACTCACGTTA AGGGATTTT AAAACATCT AAAATCAAACT TGAGTACACT TGGACCCAC 7861 GTTACCAATG CTTAATCAGT GTCAAGAGAT TCTCAGCGAT TGAGCCCTCACCC 7981 CCAGTGCTG ACTCCCCGCC GGAGACCCAC GTCTACACTAC GGAGGCCTTA CCATCTGCC 7981 CCAGTGCTG ACTCCCCGC CGAGACCCAC GTCTACCATCC 8101 AGTCTATTAA TTGTTGCCGG GAGGCCTAA CTCCACCGGC TCCACGGC TCCAGCGTTA CCATCTGGCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCCACA GTGTACATAC GGCAGTTAA TCAGCAAAAA 8041 ACCGCCCCGC CCGAAGGGCC GAAGCCACA GTGTCATCT CCATCCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCCACA GTGTCATCT CCATCCCGCC TTCAGCTCCA GCCATCTTG TCCAACGA TAAGTACTC CCCATCTTG TCCAACGA TTAACAGTC TTCAGCAATAA GTTGCCCCA ACCTTCATCCA 8221 TCAGCTCCGG TTCCCAACGA TCAAGGGCGA TTACATGGCC CCCAGTTAT AGGTTCAT 8221 TCAGCTCCGG TTCCCAACGA TCAAGGGCGA TTACATGGC CCCATGTTG TCCAAAAAG 8281 CGGTTAGCCC CTTCGGTCCT CCGATCCTT TCAGAGACTA GTGTATCAC GGCATCCTT TCAGAGACTA GTTCACCTTC TCAGAAAAAG 8281 CGGTTAGCCC GGCGCCAATA CCGGCACAT TCAAGGCGA TTACATGCC CCCATGTTG TCCAAAAAAG 8281 CGGTTAGCCC GGCGCCAATA CCGGCCCAC TTCCACCCGC CCACCATGTTG TCCAAAAAAG 8281 CGGTTAGCCC GGCGCCAATA CCGGCCACA TCCACCGC CCACCATGTTG TCCAAAAAAG 8281 CGGTTAGCCC GGCGCAATA CCGGCCAC TTACCATCCC CCCATGTTG TCCAAAAAAG 8281 CGGTTAGCCC GGCCCACA ACCAGACT TTACAGGCGA TTCAAGGCGA TTCAAGGCGA TTCAAGTCC CCCATGTTG TCCAAAAAAG GACCACCAC TCCACCAC TCC	7261	CCGCCTTTCT	CCCTTCGGGA	AGCGTGGCGC	TTTCTCAATG	CTCACGCTGT	AGGTATCTCA
7381 ACCGCTGCGC CTTATCCGGT AACTATCGTC TTGAGTCCAA CCCGGTAAGA CACGACTTAT 7441 CGCCACTGG AGCAGCCACT GGTAACAGGA TTAGCAGAGC GAGGTATGTA 7501 CAGAGTTCTT GAAGTGGTGG CCTAACTACG GCTACACTAG AAGGACAGTA TTTGGTATCT 7561 GCGCTCTGCT GAAGCCAGTT ACCTTCGGAA AAAGAGTTGG TAGCTCTTGA TCCGGCAAAC 7621 AAACCACCGC TGGTAGCGGT GGTTTTTTTG TTTGCAAGCA GCAGATTACG CGCAGAAAAA 7681 AAGGATCTCA AGAAGATCCT TTGATCTTT CTACGGGGTC TGACGCTCAG TGGAACGAAA 7741 ACTCACGTTA AGGAATTTT GTCATGAGAT TATCAAAAAA GATCTTCACC 7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TACCATTAT TGAGTAAACT TGGTCTGACA 7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGGT CTGTCTATTT CGTTCGACA 7921 TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC 7981 CCAGTGCTG AATGATACG CGAGACCCAC GCTCACCGGC TCCAGATTAT TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGGCCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8041 ACGTCTATTA TTGTTGCCGG GAAGCCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TAGATGACT GCCAGTTAAT AGTTTGCGCA 8101 AGTCTATTAA TTGTTGCCGG GAAGCCCAC GCTCACCGCC TCCAGATTAA AGTTTGCGCA 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATTCT 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATTCTT 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATTCTT TCAGCAAAAAGG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAAGAGTAA GTTGCGCCAGTTTTT 8401 TCATGGTTAT GGCAGCACTT ACCAAGTCAT TCTCAGAAATA GTTGCCCC GGCCGCCAC TTACAGCCGC TTACACGCCCA ACCAAGTCAT TCTCAGAAAAAG GTTGATCCCC CGGCCACAT TACACAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTTTC CCCAGCGCT TACACAGACC TTACACGCCCA ACCAAGTAAT CCGGGCCACA TAGCCAGAACT TTAAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTTC ACCAAGACT TTAAAAAGGGA AAAAACGGTA AAAAAGGGA AAAAAAGGGA AAAAAAGGGA AAAAAA	7321	GTTCGGTGTA	GGTCGTTCGC	TCCAAGCTGG	GCTGTGTGCA	CGAACCCCCC	GTTCAGCCCG
7501 CAGAGTTCTT GAAGTGTGG CCTAACTACG GCTACACTAG 7501 CAGAGTTCTT GAAGTGTGG CCTAACTACG GCTACACTAG 7621 AAACCACCGC TGGTAGCGGT GGTTTTTTTT TTTGGAAGCA 7681 AAGCACCGC TGGTAGCGGT GGTTTTTTT CTACGGGGT TGACGTCTA 7741 ACTCACGTTA AGGAGTTTT GTGATCTTT CTACGGGGT TGACCTCAG TGGAACGAAA 7681 TAAATTAAAA ATGAAGTTTT AAATCAATCT 7801 TAAATTAAAA ATGAAGTTTT AAATCAATCA 7781 TAGTTGCCTG ACTCCCGTC GTGTAGAAAA ATGAGTTTT TAGTATATATA 7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TAGACTAATATATA 7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TAGAGTAATAT 7801 TAAATTAAAA ATGAAGTTTT AAATCAATCA TCTCAGCGGT CTGCTTATTT CGTTCATCACA 7921 TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC 7981 CCAGTGCTGC AATGATACCG GAGGCCCAC GCTCACCGGC TCCAGATTAA TCCGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAGTAGTC GCCAGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTG TGTCAACTACG 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGGTC GCCAGTTAAT 8401 CTGTGACTG TGGAATAA CCGGCACTA TCAAGGCGAG TTACATGGTC 84401 CTGTGACTG TGGACAATA CGGGATAATA CGGCCCACA TCCAGATTA AGTTTGCGC 84401 CTGTGACTGG TGAGTACTA CCGGATAATA CGGCCCACA TCCAGATTA TCCGCAGTTTT 84401 CTGTGACTGG TGAGTACTA CCGGATAATA CCGCCCACA TAGCAGAACA TTAATCACC 8521 TCATCATTGG TAGACCACT CATAATTCTC TTACTGAAAAA GTTTGCGC CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CGGGCCACA TCCGAACATA AGCAGACTA TCTGAGAATA TCTGAGAATA TCTGAGAATA TCTGAGAATA TCTGAGAATA TCTGAGAATA CGGCCCACA TAGCAGAACT TTAAAAGTGC CAACCGACT TAGCAGAACT TTAAAAGTGC CAACCGACT TAGCAGAACT TTAAAAGTGC CAACCCACA TAGCAGAACT TTAAAAGTGC CAACCCACA TAGCAGAACT TTAAAAGTGC CAACCCACA TAGCAGAACT TTAAAAAGGGA ATTAACCCA 8641 GCGTTTCTGG GTGACCACA TCGTGCCCCA AAAAAAGGGA ATTATCACGA 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AAAGTTCTT TATTGAACC AAAAAAAGGGA ATTATCACGA 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AAAGTTCTT TATTGAACC AAAAAAAGGGA ATTATCAGGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AAAGTTCTT TATTGAACA AATTATAAA CAAATAGGGGGA TACAATAATAA AAATAGGGGGA TACAATAATAA CAAATAGGGGGA TACAATATTTA TCAACAATAAA CAAAAAAAAAA	7381	ACCGCTGCGC	CTTATCCGGT	AACTATCGTC	TTGAGTCCAA	CCCGGTAAGA	CACGACTTAT
7561 GCGCTCTGCT GAAGCAGTT ACCTTCGAA AAAGAGTTG TAGCTCTTGAAAAAAAAAA	7441	CGCCACTGGC	AGCAGCCACT	GGTAACAGGA	TTAGCAGAGC	GAGGTATGTA	GGCGGTGCTA
7561 GCGCTCTGCT GAAGCCAGTT 7621 AAACCACCGC TGGTAGCGGT 7681 AAGGATCTCA AGAAGATCCT 7741 ACTCACGTTA AGGGATTTTG 7741 ACTCACGTTA AGGGATTTTG 7801 TAAATTAAAA ATGAAGTTTT 7801 TAAATTAAAA ATGAAGTTTT 7801 TAAATTAAAA ATGAAGTTTT 7801 TAGTTGCCTG 7921 TAGTTGCCTG 7921 TAGTTGCCTG 7921 TAGTTGCCTG 7931 CCAGTGCTGC 7931 CCAGTGCTGC 7941 ACTCACGTC 7951 CCAGTGCTGC 7951 CCAGTGCTC 7951 CCAGTGCTGC 7951 CCAGTGCTGC 7951 CCAGTGCTGC 7951 CCAGTGCTC 7951 CCAGTGCTC 7951 CCAGTGCTC 7951 CCAGTGCTC 7951 CCAGTGCC 7951 CCAGTGCTC 7951 CCAGTGCTC 7951 CCAGTGCTC 7951 CCAGTGCCC 7951 CCAGTGCCC 7951 CCAGTCCTC 7951 CCAGTTCTC 7951 CCAGTCCTC 7951 CCAGTCCT	7501	CAGAGTTCTT	GAAGTGGTGG	CCTAACTACG	GCTACACTAG	AAGGACAGTA	TTTGGTATCT
7621 AAACCACCGC TGGTAGCGGT GGTTTTTTG TTTGCAAGCA GCAGATTACG CGCAGAAAAA 7681 AAGGATCTCA AGGAGATCCT TTGATCTTT CTACGGGGTC TGACGCTCAG TGGAACGAAA 7741 ACTCACGTTA AGGGATTTTG GTCATGAGAT TATCAAAAAG GATCTTCACC TAGATCCTT 7801 TAAATTAAAA ATGAAGTTTT AAATCAATCT AAAGTATATA TGAGTAACT TGGTCTGACA 7921 TAGTTGCCTG ACTCCCCGTC GTGTAGATAAA CTACGGATA CTGTCTATTT CGTTCATCCA 7981 CCAGTGCTGC AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGCCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8101 AGTTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA 8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT 8221 TCAGCTCCGG CTTCCAACCAG TCAAGGGGG TGCATTTATTCC GCCTCCATCC 8221 TCAGCTCCGG CTTCCGGTCCT CTCCAGCGA TCACAGGAGT TCAAGGCGAG TTCACAGGAT CCCCCATGTT TCCAAAAAAG 8281 CGGTTAGCT CTTCCGGTCCT CATCGGTCC TCAAGCAGAT TCAGGAAGTA GTTGGCCGC GTGTTATCAC 8341 TCATGGTTAT GGCAGCACT CCGATCGTT TCAGAAGTA GTTGGCCGC GTGTTATCAC 8341 TCATGGTTAT GGCAGCACT CCGATCGTT TCAGAAGTA GTTGGCCGC GTGTTATCAC 8461 GCTCTTGCC GGCGCAATA CCGGCGCACA TCGAGAAAT GTGTATCCG CGACCGAGTT 8401 CTGTGACTGG GTGAGCAAAA ACCCACT TCTGAGAATA GTTGGCCGC CGACCGAGTT 8401 CTGTGACTGG GTGAGCAAAA ACCCAAGTCAT TCTGAGAATA GTGTTATCCG CGACCGAGTT 8401 CCAGTTCGT GTGAGCAAAA ACCCACCA ACTGATCTTC AGCATCCTT TAAAAGTGC 8521 TCATCATTGG GAGCACAC CGGGGCGAA AACTCTCAAG GATCTTTCACCA ACCAAGTCAT TCTGAGAAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG GAGCAAAA ACCCACC CGTGTCACCCA ACTGATCTTC AAAAAAGGGA AAAAACGTTCT TCGGGCGAAAAAAAACGTTCT TCGGGCGCAAAAAAAAGCGC AAAAAAGGGA AAAAACGCT TTAAAAGGGGA 8641 GCGTTTCTGG GTGAGCAAAA ACCCCCA ACTGATCTTC AAAAAAAGGGA ATAAAGGCGA 8761 GTTATTGTCT CATGAGCGGA TACCTCTCC TTTTTCAATA TTATTGAAGG ATTTATCAGGGA 8761 GTTATTGTCT CATGAGCGGA TACCTCTTC TTTTTCAATA TTATTGAAGG ATTTATCAGGGA 8761 GTTATTGTCT CATGAGCGGA TACCTCTTC TTTTTTCAATA TTATTGAAGG ATTTATCAGGGA 8761 GTTATTGTCT CATGAGCGGA TACCTCTTC TTTTTTTTTT	7561	GCGCTCTGCT	GAAGCCAGTT	ACCTTCGGAA	AAAGAGTTGG	TAGCTCTTGA	TCCGGCAAAC
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7741 ACTCACGTTA AGGGATTTTG GTCATGAGAT TATCAAAAAG GATCTTCACC TAGATCCTTT 7801 TAAATTAAAA ATGAAGTTTT AAATCAATCT AAAGTATATA TGAGTAAACT TGGTCTGACA 7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGAT CTGTCTATTT CGTTCATCCA 7921 TAGTTGCCTG ACTCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC 7981 CCAGTGCTGC AATGATACCG CGGAGACCCAC GCTCACCGGC TCCAGGTTTA TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAAGGCAGA GTGGTCCTGC AACTTTATCC GCCTCCATCC 8101 AGTCTATTAA TGTTGCCGG GAAGGCAGA GTGGTCCTCC GCCAGGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTATC GCCTCCATCC 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTTGCGCA 8341 TCATGGTTAT GGCAGCACT CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG GGCGCACATA ACCAAGTCAT TCTGAGAATA GTTTGCCG CGACCGAGTT 84401 CTGTGACTGG GGCGCACATA ACCAAGTCAT TCTGAGAATA GTTTGCCG CGACCGAGTT 84401 CTGTGACTGG GGCGCACATA ACCAAGTCAT TCTGAGAATA GTTTGCCG CGACCGAGTT 84401 CTGTGACTGG GGCGCACATA ACCAAGTCAT TCTGAGAATA GCCATCCGTA AGATGCTTTT 84401 CTGTGACTGG GGCGCACATA ACCAAGTCAT TCTGAGAATA ACCACCCA ACTGATCTTC AAAAAAGGGA ATAAAGGGA ACTGTTCAACCA ACAAAAAGGGA AAAAAAGGGA ACTGTTCAACCA AAAAAAGGGA ACTGTCAATA ACAAGGAAGGA ACTGTTCAATA ACTTTCAACA ACAAGGAAGGC AAAATGCCC AAAAAAAGGGA ATAAGGGGGA ATATTTCAGGCGA ACTGTTTTTTTTTT	7681	AAGGATCTCA	AGAAGATCCT	TTGATCTTTT			
7801 TAAATTAAAA ATGAAGTTTT AAATCAATCT AAAGTATATA TGAGTAAACT TGGTCTGACA 7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGAT CTGTCTATTT CGTTCATCCA 7921 TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC 7981 CCAGTGCTGC AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAAG 8281 CGGTTAGCTC CTTCGGTCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATAA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTTC CTGTTAGAGT 8581 CCAGTTCGG GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTT ACTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGGAAGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTC TTTTTCCAATA TTATTGAAGC ATTTATCACG 8761 GTTATTGTCT CATGAGCGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGGA	7741	ACTCACGTTA	AGGGATTTTG				
7861 GTTACCAATG CTTAATCAGT GAGGCACCTA TCTCAGCGAT CTGTCTATTT CGTTCATCCA 7921 TAGTTGCCTG ACTCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC 7981 CCAGTGCTGC AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC 8101 AGTCTATTAA TTGTTGCCG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTT AGCAGAACT TTAAAAGTGC 8521 TCATCATTGG GTAACCCACT CGTGCACCCA ACTGATCTT AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGA TACATATTTG AATGTATTAA GAAAAATAAA CAAATAGGGG	7801	TAAATTAAAA	ATGAAGTTTT	AAATCAATCT	AAAGTATATA	TGAGTAAACT	TGGTCTGACA
7921 TAGTTGCCTG ACTCCCCGTC GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC 7981 CCAGTGCTGC AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTAGT ATGGCTTCAT 8221 TCAGCTCCGG TCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTTCACCA 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGA TACATATTTG AATGTATTTA GAAAAATAAA CAAAATAGGGGA	7861	GTTACCAATG	CTTAATCAGT	GAGGCACCTA	TCTCAGCGAT	CTGTCTATTT	CGTTCATCCA
7981 CCAGTGCTGC AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTA TCAGCAATAA 8041 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT 8221 TCAGCTCCGG TCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGAA TACATATTTG AATGTATTTA GAAAAATAAA CAAAATAGGGGG	7921	TAGTTGCCTG	ACTCCCCGTC	GTGTAGATAA	CTACGATACG	GGAGGGCTTA	CCATCTGGCC
8041 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCCTGC AACTTTATCC GCCTCCATCC 8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT 8221 TCAGCTCCGG TCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGA TACATATTTG AATGTATTTA GAAAAATAAA CAAAATAGGGG	7981	CCAGTGCTGC	AATGATACCG	CGAGACCCAC	GCTCACCGGC	TCCAGATTTA	TCAGCAATAA
8101 AGTCTATTAA TTGTTGCCGG GAAGCTAGAG TAAGTAGTTC GCCAGTTAAT AGTTTGCGCA 8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT 8221 TCAGCTCCGG TCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGGG	8041	ACCAGCCAGC	CGGAAGGGCC	GAGCGCAGAA	GTGGTCCTGC	AACTTTATCC	GCCTCCATCC
8161 ACGTTGTTGC CATTGCTACA GGCATCGTGG TGTCACGCTC GTCGTTTGGT ATGGCTTCAT 8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8101	AGTCTATTAA	TTGTTGCCGG	GAAGCTAGAG	TAAGTAGTTC	GCCAGTTAAT	AGTTTGCGCA
8221 TCAGCTCCGG TTCCCAACGA TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAAG 8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGGG	8161	ACGTTGTTGC	CATTGCTACA	GGCATCGTGG	TGTCACGCTC	GTCGTTTGGT	ATGGCTTCAT
8281 CGGTTAGCTC CTTCGGTCCT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC 8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGGG	8221	TCAGCTCCGG	TTCCCAACGA	TCAAGGCGAG	TTACATGATC	CCCCATGTTG	TGCAAAAAAG
8341 TCATGGTTAT GGCAGCACTG CATAATTCTC TTACTGTCAT GCCATCCGTA AGATGCTTTT 8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8281	CGGTTAGCTC	CTTCGGTCCT	CCGATCGTTG	TCAGAAGTAA	GTTGGCCGCA	GTGTTATCAC
8401 CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA GTGTATGCGG CGACCGAGTT 8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8341	TCATGGTTAT	GGCAGCACTG	CATAATTCTC	TTACTGTCAT	GCCATCCGTA	AGATGCTTTT
8461 GCTCTTGCCC GGCGTCAATA CGGGATAATA CCGCGCCACA TAGCAGAACT TTAAAAGTGC 8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8401	CTGTGACTGG	TGAGTACTCA	ACCAAGTCAT	TCTGAGAATA	GTGTATGCGG	CGACCGAGTT
8521 TCATCATTGG AAAACGTTCT TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT 8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8461	GCTCTTGCCC	GGCGTCAATA	CGGGATAATA	CCGCGCCACA	TAGCAGAACT	TTAAAAGTGC
8581 CCAGTTCGAT GTAACCCACT CGTGCACCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA 8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8521	TCATCATTGG	AAAACGTTCT	TCGGGGCGAA	AACTCTCAAG	GATCTTACCC	CTGTTCAGAT
8641 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA ATAAGGGCGA 8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8581	CCAGTTCGAT	GTAACCCACT	CGTGCACCCA	ACTGATCTTC		
8701 CACGGAAATG TTGAATACTC ATACTCTTCC TTTTTCAATA TTATTGAAGC ATTTATCAGG 8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8641	GCGTTTCTGG	GTGAGCAAAA	ACAGGAAGGC	AAAATGCCGC	AAAAAAGGGA	ATAAGGGGGA
8761 GTTATTGTCT CATGAGCGGA TACATATTTG AATGTATTTA GAAAAATAAA CAAATAGGGG	8701	CACGGAAATG	TTGAATACTC	ATACTCTTCC	THE TOUCHC		
8821 TTCCGCGCAC ATTTCCCCGA AAAGTGCCAC CTGACGTC	8761	GTTATTGTCT	CATGAGCGGA	TACATATTTC	AATGTATTTA	CIAILGRAGE	CAAATAGGGG
	8821	TTCCGCGCAC	ATTTCCCCGA	AAAGTGCCAC	CTGACGTC	HHHHHHHH	Doomana

FIG. 14C

O HE: **-**0 20 30 4 RVSLSC<u>RASOSISDYLH</u>WYQQKS ŤLSC<u>RASOSVSSYLA</u>WYQQKP ERA Ω. P G 1 Ö Д LS 1 DIVLTQSPATLSVT ß ᇊ K IVLTQSP

80 90 100 SVEPEDVGIYYC<u>OHGHSFPWT</u>FGGGTKLE | | | | | EDFAVYYC<u>OORSNWPLT</u>FGGGTKV Д 더 SL 70 SDFTLSINS FTLŤIS Ω - E-I Ü ŋ Ø S G Ŋ Ŋ S Ü G Ø Ø 60 IPSRF Ľ 出 ď IP 50 YASHSISGI ß DASNRAT

VH Domain

\* E 40 OEMPGF CKASGYTFT<u>SYAMN</u>WVRQAPGU 1 QIQLVQSGPELKKPGFTVRISCKASGYAFT<u>TTGMO</u>WV Ŋ ELKKPGASVKV. QVQLVQSG CD40 VH7

SLKAEDTAVYYCA 80 abc 90 ANTAYLQISNLKNEDTATYFC AYLQIS SVST S 70 AFSLETS SLDT V F : WINTHSGVPKYVEDFKGRF WINTNTGNPTYAOGFTGRF CD40 VH7

0 9

 $\alpha$ 

- ഗ 0 8 GNGNYDLAYFAYWGQGTLVTV Φ abcd

CD40

JH4

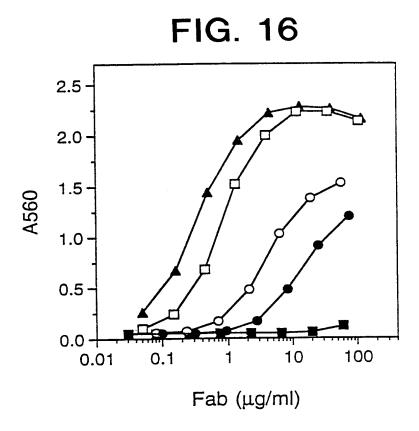


FIG. 17

